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시계열분석을 활용한 페로니켈 공장의 지역사회 건강영향 평가

Adverse health effects of ferronickel manufacturing factory on local residents
:An interrupted time-series analysis

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서울대학교 대학원
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한 창 우

A thesis of Degree of Doctor of Philosophy

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Adverse health effects of ferronickel manufacturing factory on local residents :An interrupted time-series analysis

by

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A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Medicine (Preventive Medicine) at Seoul National University College of Medicine

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Abstract

Adverse health effects of ferronickel manufacturing factory on local residents : An interrupted time-series analysis

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Backgrounds: The first ferronickel manufacturing factory of the Republic of Korea was opened in Gwangyang City on October, 2008. There has been public concern regarding heavy metal dust blown from the factory and slag disposal site. Therefore, we evaluated the health impact of the ferronickel factory on Gwangyang City residents by using interrupted time-series analysis.

Materials and methods: We analyzed the monthly incidence patterns of asthma, allergic rhinitis, and dermatitis in Gwangyang City residents from 2004 to 2014. Data were gathered from the National Health Insurance Service database which covers all the hospital use data of entire city residents. Seasonality adjusted quasi-Poisson regression model was used to evaluate whether the operation of the ferronickel factory was associated with the immediate changes in the monthly disease incidence patterns. We set a control

region, Yeosu City, near Gwangyang City to ensure that the changes in the disease incidence were specific to Gwangyang City. We conducted sub-regional level analysis to evaluate whether the disease incidence patterns were affected by the distance from the ferronickel factory.

Results: The risk estimates after operation of the ferronickel factory showed an abrupt increase in the monthly incidence of unspecified contact dermatitis [RR (95% CI), 1.75 (1.17-2.60)] and vasomotor and allergic rhinitis [RR (95% CI), 1.23 (1.08-1.39)] in men, and pruritus [RR (95% CI), 1.95 (1.51-2.52)], unspecified contact dermatitis [RR (95% CI), 1.65 (1.04-2.60)], and vasomotor and allergic rhinitis [RR (95% CI), 1.17 (1.04-1.31)] in women. These findings were significant even after accounting for the changes of the corresponding disease incidence of the comparison city, Yeosu. The effects were greater in young children (aged 0-9) and sub-regions near the ferronickel factory.

Conclusions: Our study suggests possible association between the operation of the ferronickel factory and an abrupt increase of pruritus, unspecified contact dermatitis, and vasomotor and allergic rhinitis in Gwangyang City residents. Future community-based epidemiological investigation is needed in Gwangyang City to confirm our study findings.

Keywords: Ferronickel factory; Nickel; Interrupted time-series; Pruritus; Dermatitis; Rhinitis

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Contents

List of Tables

List of Figures

Introduction

The first ferronickel manufacturing factory of the Republic of Korea was opened in Gwangyang City's industrial complex on October, 2008. The factory produces 30,000 tons of ferronickel products annually, which is used as the raw material for manufacturing stainless steel. As a by-product of ferronickel, slag is produced when nickel ore and bituminous coal are heated to a high temperature in an electric arc furnace (Demotica et al. 2012). Since its operation, the factory has produced a total of 8 million tons of slag, 4.2 million of which has been used as engineering aggregates. However, the remaining 3.8 million tons of slag is dumped at a waste disposal site near the factory without proper treatment.

The public has raised concerns regarding the adverse health effects of dust blown from the ferronickel factory and slag disposal site. Ferronickel slag contains diverse toxic substances such as silica and chromium in addition to iron and nickel (Demotica et al. 2012). The literature shows that high levels of nickel have been detected in the air, dust, soil, and water sediments near the ferronickel mines in Columbia (Marrugo-Negrete et al. 2017; Marrugo-Negrete et al. 2014). High levels of chromium, cobalt and other heavy metals, as well as nickel, were also detected in the atmosphere, soil, and dust near a ferronickel smelter plant in the Republic of Macedonia (Bačeva et al. 2012; Boev et al. 2013). Micrometer-sized serpentine mineral dust can also be generated during the nickel ore crushing process at the ferronickel smelting factory (Boev et al. 2013).

In the occupational setting, exposure to airborne nickel, chromium, and cobalt are reported to be associated with dermatitis and asthma (Fernandez-Nieto et al. 2006; Huygens and Goossens 2001). Among children, exposure to nickel in ambient air has been associated with nickel sensitization (Mann et al. 2010). Micrometer-sized serpentine mineral dust can be retained in the air for a long period and transported easily by the wind, thereby affecting the mineralogical composition of airborne particles near ferronickel factories (Boev et al. 2013). According to previous reports, exposure to dust containing diverse heavy metals was associated with an abrupt increase in the number of hospital visits due to asthma, allergic rhinitis, and conjunctivitis (Otani et al. 2012). Exposure to ferronickel slag dust may also cause skin irritation due to its alkaline pH and crystalline, glassy, and rough nature (Demotica et al. 2012).

A chemical composition analysis using X-ray fluorescence revealed that the ferronickel slag from the Gwangyang ferronickel factory's waste disposal site contained diverse metals including nickel, chromium, cobalt, iron, copper, and lead, in addition to silica and magnesium (Table 1). According to the Pollutant Release and Transfer Registry (Ministry of Environment 2018), amount of nickel waste transfer in Gwangyang City increased by 246 times from 1,172 kg in year 2008 to 288,542 kg in year 2009, just after the operation of the ferronickel factory (Figure 1). The amount of air emissions of nickel and nickel compounds in Gwangyang City was 9 times higher in year 2010 (5,012 kg) compared to year 2008 (528 kg) (Figure 2). The amount of air emissions of chromium and chromium compounds in Gwangyang City

was 21.6 times higher in year 2010 (4,373 kg) compared to year 2008 (202 kg) (Figure 2).

After monitoring the heavy metal contents of particulate matter in the year 2016 (7 consecutive days per season), the levels of nickel, chromium, and cobalt were found to be higher in Gwangyang City than the nearest industrial city, Yeosu (Table 2 and Figure 3) (National Institute of Environmental Research (NIER) 2017). In addition, ferrous and nickel contents of particulate matter in sub-regions of Gwangyang City were higher than any other sub-regions which are located near other industrial complexes of Korea. Although cautious interpretation is needed for the Pollutant Release and Transfer Registry and air monitoring results, it is reasonable to speculate that the operation of the ferronickel factory and dumping of ferronickel slag may affect the heavy metal content of airborne particles near the ferronickel factory.

The National Institute of Environmental Research initiated the project to monitor the health status of the residents living near the industrial complex of Gwangyang City. During the eight years of study period, the project found that the residents living near the industrial complex showed a higher prevalence of allergic diseases such as allergic rhinitis and conjuntivitis compared to the residents living far from the industrial complex (National Institute of Environmental Research (NIER) 2010; 2012). However, causal interpretation was limited due to the lack of longitudinal study design and improper use of analysis methods. In addition, the association between specific event occurred in the industrial complex (e.g. operation of the factory) and adverse health outcomes of residents has never been evaluated.

Therefore, by using a quasi-experimental method, an interrupted time-series analysis, we tried to evaluate whether the monthly incidence patterns of asthma, allergic rhinitis, and dermatitis in Gwangyang City residents had changed after the operation of the ferronickel factory. Our main hypothesis was abrupt increase of irritant or allergic disease incidence of Gwangyang City residents after the operation of the ferronickel factory, due to dust originating from the factory and slag disposal site. To strengthen causal inferences, we additionally assessed the same association in a comparison city (Yeosu) near Gwangyang City. The sub-regional level analysis in Gwangyang City was also conducted to evaluate whether the disease incidence patterns were affected by the distance from the ferronickel factory.

Table 1. Heavy metal contents in granulated and air-cooled ferronickel slag from the Gwangyang City ferronickel factory.

Types of Ferronickel Slag	Cd	Cu	Pb	Zn	Ni	As	Hg	Cr (6^+)
Examined by NIER[a] (mg/kg)								
Granulated slag	0.94	2.4	14.3	95.1	881.4	N.D[c]	N.D	0.5
Air cooled slag	0.37	1.9	8.0	57.7	477.0	N.D	N.D	0.9

	SiO_2	Fe_2O_3	MgO	CaO	Al_2O_3	MnO	Cr_2O_3	SO_3	P_2O_5	ZnO	TiO_2	NiO	K_2O	V_2O_5	Co_3O_4	NaO	Cl
Examined by GIST[b] (%)																	
Granulated slag	41.74	21.83	18.36	7.85	5.79	1.02	1.00	0.75	0.44	0.32	0.25	0.25	0.22	0.05	0.04	0.03	0.02
Air cooled slag	51.72	14.98	27.81	0.32	1.56	0.50	1.55	0.44	0.01	0.04	0.03	0.13	0.04	0.02	0.03	0.70	0.11

[a] NIER: National Institute of Environmental Research
[b] GIST: Gwangju Institute of Science and Technology
[c] N.D: Not Detected

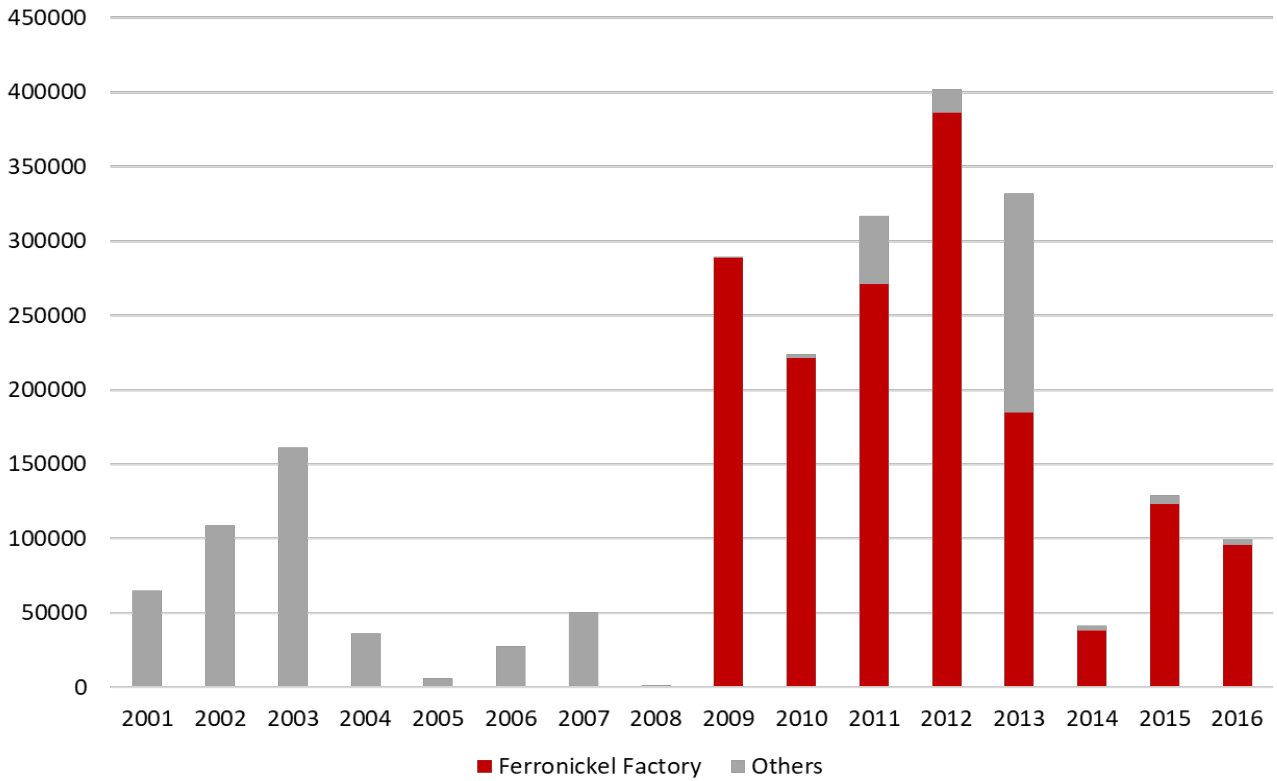


Figure 1. Amount (kg) of Nickel waste transfer, Gwangyang City (Data are from the Pollutant Release and Transfer Registry (Ministry of Environment 2018))

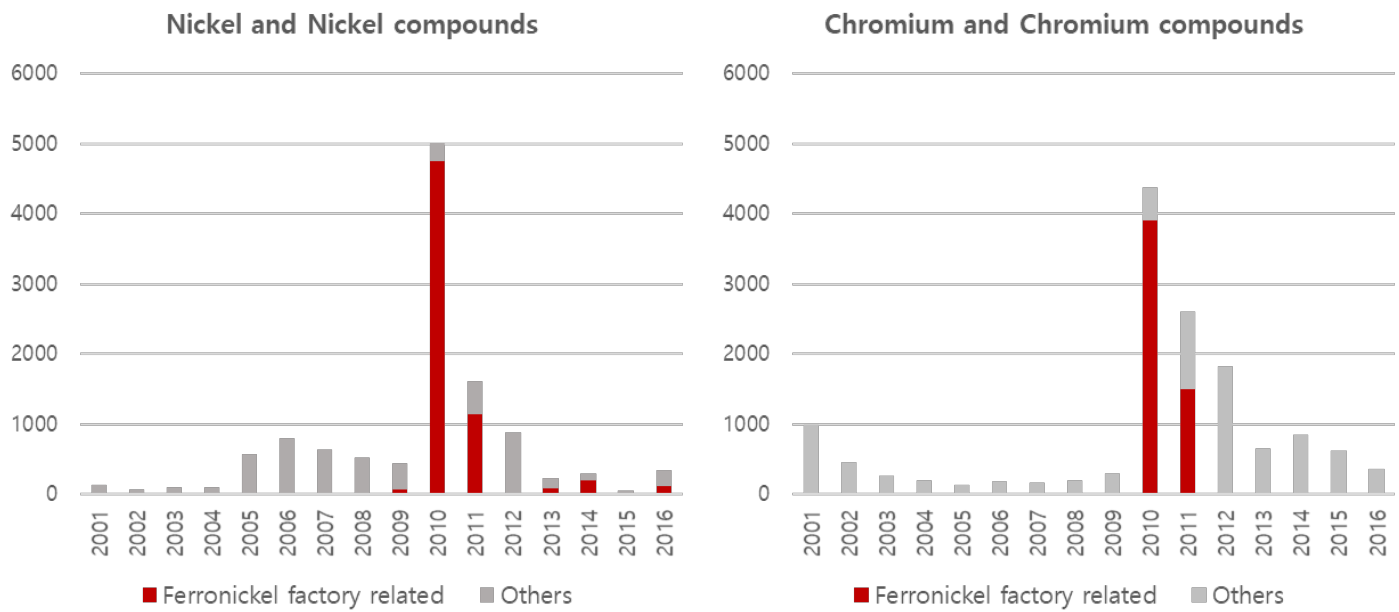


Figure 2. Amount (kg) of air emission of Nickel and Nickel compounds, and Chromium and Chromium compounds, Gwangyang City (Data are from the Pollutant Release and Transfer Registry (Ministry of Environment 2018))

Table 2. Heavy metal contents[a] (ng/m^3) of particulate matter in the year 2016 at Gwangyang and Yeosu City. This table was constructed based on the report from the National Institute of Environmental Research (National Institute of Environmental Research (NIER) 2017).

Heavy metals	Gwangyang		Yeosu	
	Taein-dong	Geumho-dong	Haesan-dong	Jusam-dong
As	11.0	11.2	5.7	7.9
Be	N.D[b]	N.D	N.D	N.D
Cd	0.5	0.6	0.5	0.7
Co	1.1	0.4	0.3	0.4
Cr	47.4	48.7	9.9	10.4
Fe	2327.4	2340.3	1249.1	1498.8
Mn	56.1	54.5	34.9	41.0
Ni	22.0	22.5	12.2	15.0
Pb	35.7	39.7	36.4	37.7
Zn	1478.0	1485.5	546.1	560.6
V	N.D	N.D	N.D	N.D

[a] Heavy metal contents were analyzed by Inductively Coupled Plasma/Atomic Emission Spectrometer
[b] N.D, Not detected

Figure 3. Location of monitoring stations of Table 2

Material and Methods

Study design

We performed an interrupted time-series analysis to evaluate whether the operation of the ferronickel manufacturing factory and ferronickel slag dumping affected the incidence of adverse health outcomes. Interrupted time-series analysis is a useful quasi-experimental method of evaluating the effectiveness of an intervention or event at the population level.

A time-series refers to a series of observations made on the same variable recorded at equal intervals. The patterns of time-series outcomes show changes (interrupted) when the event or intervention has impacts on the outcome. By comparing the post-intervention time-series outcome with counterfactual outcome under the hypothetical scenario with no intervention or events, we would be able to assess the impacts of intervention or event (Bernal et al. 2016).

One of the major threats to the internal validity of an interrupted time-series analysis is the existence of other factors affecting the time-series outcome at the same time at which the intervention or event occurred. Therefore, to strengthen causal inference in our analysis, we added several design features to the basic structure of an interrupted times series analysis (Lopez Bernal et al. 2018). First, we added a health outcomes (fracture of the forearm and osteoporosis without pathological fracture) which are hypothesized to be irrelevant to the operation of the ferronickel factory or exposure to ferronickel slag dust. Second, we set a socioeconomically and geographically

similar control region (Yeosu City) and evaluated the same association to prove that the disease incidence patterns in the control region had not been affected by the ferronickel factory operation. Last, we conducted additional sub-regional level analysis in Gwangyang City to prove the hypothesis that people residing near the ferronickel factory may be more affected than those residing in far sub-regional administrative districts.

Study areas

Gwangyang City (with an area of 458.89 km^2) is an industrial city located in the southernmost part of the Republic of Korea (Figure 4). The comparison city Yeosu (with an area of 510.09 km^2) is a neighboring industrial city located on the southern side of Gwangyang City. The Gwangyang Bay locates between the Gwangyang and Yeosu City. According to the National Statistical Office of the Republic of Korea, 144,414 and 273,761 residents lived in Gwangyang and Yeosu City in 2015, respectively.

The national industrial complex of Gwangyang and Yeosu City are located near the Gwangyang Bay. The major industries of Gwangyang City industrial complex are steel mill, mechanical, and non-metal industries and major industries of Yeosu City industrial complex are petrochemical and other related industries (National Institute of Environmental Research (NIER) 2017). Because of the air pollution (ozone, volatile organic compounds, hazardous air pollutants, and odor) originating from the

Gwangyang and Yeosu City industrial complexes, the Gwangyang Bay was designated as “Air Quality-Regulated Area” in year 1999 according to the Clean Air Conservation Act.

The ferronickel factory and waste disposal site are located at Geumho-dong, inside the Gwangyang City industrial complex (Figure 4). Because the Gwangyang Bay locates between Gwangyang and Yeosu City and the main residential area of Yeosu City is located in the southern part of Yeosu City, we hypothesized that the effects of ferronickel factory operation and ferronickel slag dumping was limited to Gwangyang City residents, and we set Yeosu City as a control region for our analysis.

If the effects of the ferronickel factory operation and ferronickel slag dumping were mediated by the airborne dust, the effects would be greater in the sub-regional administrative districts near the ferronickel factory compared to the sub-regional districts located far from the factory. Therefore, we selected the three sub-regional administrative districts of Gwangyang City to perform the sub-regional level analysis. To secure enough incident cases for each disease outcome, we selected the three highest populated sub-regions where the mean yearly populations were over 15,000. We divided the selected sub-regional districts into the near (within 10km, Jungma-dong, Geumho-dong) and far (over 15km, Gwangyang-eup) regions from the ferronickel factory site. Demographics and basic characteristics of Gwangyang and Yeosu cities, as well as sub-regions of Gwangyang City are summarized in Table 3.

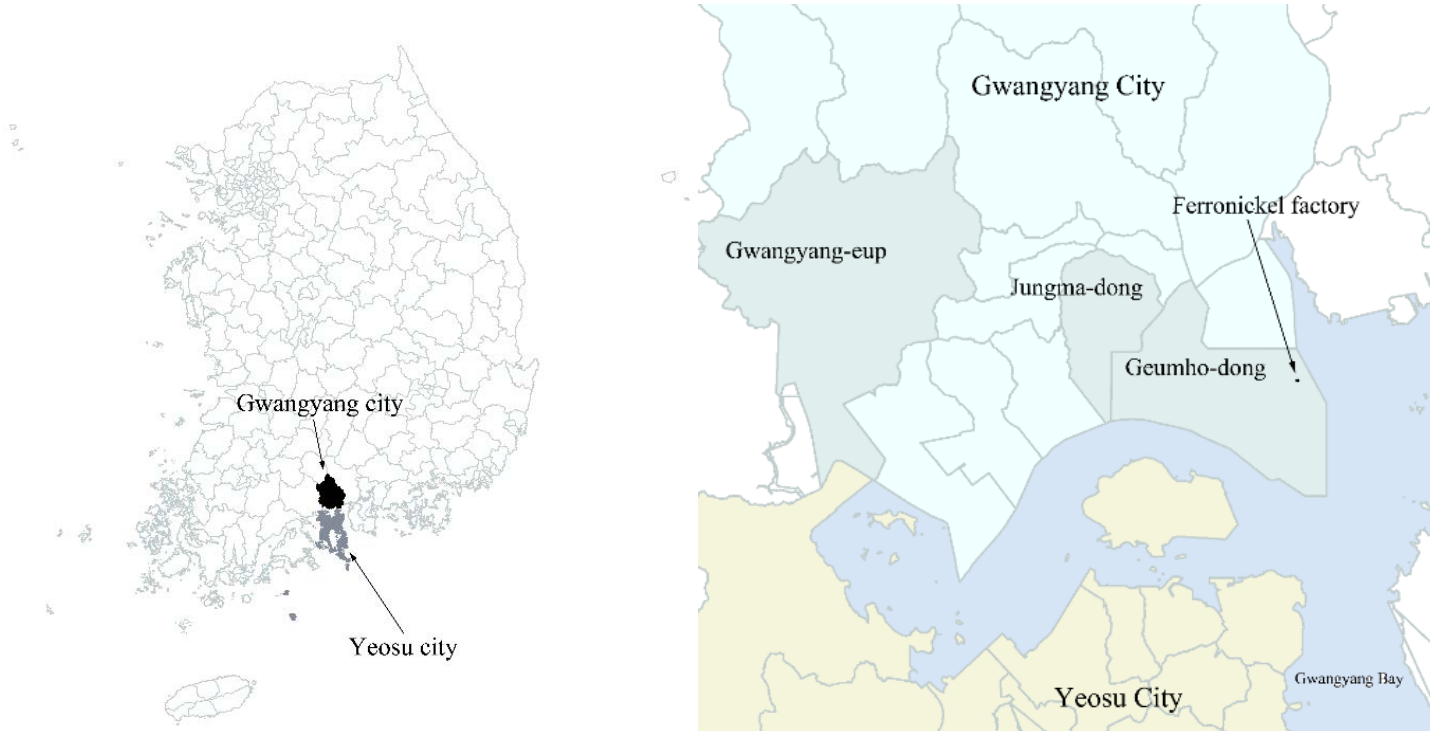


Figure 4. Map of the study area, including Gwangyang City and the comparison City, Yeosu. Sub-regional administrative districts of Gwangyang City (Jungma-dong, Geumho-dong, and Gwangyang-eup) are also included.

Table 3. Characteristics of Gwangyang and Yeosu City in year 2014 (All the data are gathered from Statistics Korea homepage[a]).

			Sub-regions of Gwangyang		
	Gwangyang	Yeosu	Gwangyang-eup	Jungma-dong	Geumho-domg
Area (km^2)	460	510	55	10	21
Mid-year registered residents (number)					
Total	151,261.0	289,248.5	48,974	53,440	14,429
Less than 9 years, n (%)	16,310 (10.78)	25,439.5 (8.80)	5,517 (11.27)	7,476 (13.99)	996 (6.9)
10 to 29 years, n (%)	40,888 (27.03)	71,366 (24.67)	12,496 (25.52)	15,417 (28.85)	5,334 (36.97)
30 to 59 years, n (%)	72,905 (48.20)	133,716 (46.23)	23,446 (47.87)	27,487 (51.44)	6,978 (48.36)
Equal to or more than 60 years of age, n (%)	21,158 (13.99)	58,727 (20.30)	7,515 (15.34)	3,060 (5.73)	1,121 (7.77)
Population density (thousands/km^2)	0.33	0.57	0.89	5.34	0.69
Gross regional domestic product per capita (1,000,000 Korean Won)	9,950,509	18,262,290			
Meteorological factors (Annual mean)					
Temperature (˚C)	14.4	14.7			
Relative Humidity (%)	63.8	60.0			
Characteristics related to hospital use					
General hospital (Number)	1	3	0	1	0
Hospital (Number)	3	6	1	2	0
Clinic (Number)	51	139	16	24	1
Number of doctors	106	372	20	72	4

[a] http://kostat.go.kr/portal/korea/index.action

Basic characteristics of the ferronickel manufacturing factory

The ferronickel manufacturing factory at Gwangyang City released the first ferronickel products on October, 2008. Annually, the factory produces 30,000 tons of ferronickel products and 1 million tons of ferronickel slag. The general features of the ferronickel manufacturing process are as follows: nickel ore transported from New Caledonia is mixed and put in a dryer to remove the moisture. After drying, the ore goes through the preliminary reduction process to eliminate oxygen in nickel and iron. With additional smelting and reduction processes in an electric arc furnace, ferronickel molten iron and slag are produced. After the final casting, ferronickel molten iron is manufactured as ferronickel products in the form of Luppe. As a by-product of ferronickel production, ferronickel slag is produced when nickel ores are treated with a high temperature in an electric arc furnace. With natural air cooling or spraying of water, smelting slag becomes air-cooled slag and granulated slag. Granulated slag can easily be broken into small particles and used as concrete sand. Air-cooled slag is crushed and used as engineering aggregates.

Outcomes Measure

We used the customized health information data provided by the National Health Insurance Service, which covers almost all the hospital use data of the Republic of Korea. The National Health Insurance Service created the National Health Insurance Database (NHID) for academic or administrative use of health insurance information.

From the NHID, we obtained hospital use data of the Gwangyang and Yeosu City residents from 2002 to 2014, whose primary diagnosis codes were as follows: disease (*International Classification of Disease, 10th revision code*), (a) acute bronchitis (J20.X-J22.X), (b) asthma (J45.X), (c) vasomotor and allergic rhinitis (J30.X), (d) atopic dermatitis (L20.X), (e) seborrheic dermatitis (L21.X), (f) allergic contact dermatitis (L23.X), (g) irritant contact dermatitis (L24.X), (h) unspecified contact dermatitis (L25.X), (i) pruritus (L29.X), (j) other dermatitis (L30.X), (k) Malignant neoplasm of bronchus and lung (C34.X) (l) fracture of forearm (S52.X) and (m) osteoporosis without pathological fracture (M81.X). Diseases (a)-(k) were selected based on prior literature reviews (Fernandez-Nieto et al. 2006; Huygens and Goossens 2001; Otani et al. 2012), suggesting their possible association with heavy metal dust exposure, particularly nickel. Disease (l)-(m) were selected as a control outcomes because it was hypothesized to be irrelevant to the ferronickel factory operation or exposure to ferronickel slag dust.

We first extracted the data of the initial hospital visit (incidence data) for each disease outcome for persons who resided in Gwangyang or Yeosu City. To capture actual incidence cases, we deleted the incidence data when the initial hospital visits occurred from 2002 to 2003, thereby leaving the incidence cases of Gwangyang and Yeosu City residents for each disease outcome from 2004 to 2014. Therefore, a person who was diagnosed with a certain disease outcome in November 2008 in our incidence data is a person who had not been diagnosed with that disease from January 2002 to October 2008.

To calculate the monthly incidence rate (per 100,000 persons), we divided the number of monthly disease incidence cases by the number of yearly eligible persons who retained eligibility criteria for the health insurance service of the corresponding city or sub-region. We age-standardized the incidence rate by using the World Health Organization standard population and direct age standardization method (Boyle and Parkin 1991). For the intuitive understanding of readers, we multiplied each monthly incidence rate in our figures and tables by 100,000. Number of yearly eligible person who retained eligibility criteria for the health insurance service for Gwangyang City and sub-regions of Gwangyang City are presented at Table 4.

The institutional review board of the Seoul National University Hospital, Republic of Korea, exempted this study from review because we used customized de-identified health information data provided by the National Health Insurance Service (IRB no. E-1609-010-789). To protect personal information, our analysis was conducted at the population level with minimal personal data such as sex, age, and sub-regional level addresses.

Table 4. Number of eligible person who retained eligibility criteria for the health insurance service in Gwangyang and Yeosu City.

Year	Total	Age group, N (%)								
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-
Gwangyang City										
2002	135304	24620 (18.2)	20006 (14.79)	18887 (13.96)	28588 (21.13)	19765 (14.61)	9387 (6.94)	8004 (5.92)	4362 (3.22)	1685 (1.25)
2003	134479	22998 (17.1)	20214 (15.03)	18213 (13.54)	28034 (20.85)	20723 (15.41)	9819 (7.3)	8124 (6.04)	4533 (3.37)	1821 (1.35)
2004	135989	22048 (16.21)	20926 (15.39)	17861 (13.13)	27890 (20.51)	21661 (15.93)	10744 (7.9)	8129 (5.98)	4871 (3.58)	1859 (1.37)
2005	137149	20387 (14.86)	21957 (16.01)	17774 (12.96)	26965 (19.66)	22834 (16.65)	11942 (8.71)	8058 (5.88)	5281 (3.85)	1951 (1.42)
2006	137070	19198 (14.01)	22625 (16.51)	17324 (12.64)	25682 (18.74)	23887 (17.43)	12647 (9.23)	7986 (5.83)	5716 (4.17)	2005 (1.46)
2007	146340	18219 (12.45)	24307 (16.61)	19019 (13)	25040 (17.11)	25623 (17.51)	13922 (9.51)	10124 (6.92)	7569 (5.17)	2517 (1.72)
2008	148937	17601 (11.82)	24994 (16.78)	19348 (12.99)	24005 (16.12)	27153 (18.23)	14928 (10.02)	10220 (6.86)	7981 (5.36)	2707 (1.82)
2009	150932	16924 (11.21)	25332 (16.78)	19368 (12.83)	23556 (15.61)	28157 (18.66)	16035 (10.62)	10195 (6.75)	8391 (5.56)	2974 (1.97)
2010	145591	16194 (11.12)	24842 (17.06)	17695 (12.15)	22770 (15.64)	28172 (19.35)	17377 (11.94)	8846 (6.08)	6838 (4.7)	2857 (1.96)
2011	148462	16067 (10.82)	24314 (16.38)	18784 (12.65)	22866 (15.4)	28764 (19.37)	18873 (12.71)	8989 (6.05)	6851 (4.61)	2954 (1.99)
2012	151174	16356 (10.82)	23890 (15.8)	18751 (12.4)	22803 (15.08)	29057 (19.22)	20304 (13.43)	9432 (6.24)	7303 (4.83)	3278 (2.17)
2013	152106	16372 (10.76)	22903 (15.06)	18745 (12.32)	22502 (14.79)	29190 (19.19)	21717 (14.28)	9769 (6.42)	7429 (4.88)	3479 (2.29)
2014	152738	16221 (10.62)	21743 (14.24)	19368 (12.68)	21967 (14.38)	28975 (18.97)	22665 (14.84)	10651 (6.97)	7426 (4.86)	3722 (2.44)
Yeosu City										

2002	306706	41982 (13.69)	44829 (14.62)	50554 (16.48)	50518 (16.47)	47812 (15.59)	32084 (10.46)	22852 (7.45)	11836 (3.86)	4239 (1.38)
2003	303273	39674 (13.08)	43496 (14.34)	48822 (16.1)	49807 (16.42)	49119 (16.2)	32362 (10.67)	23320 (7.69)	12014 (3.96)	4659 (1.54)
2004	299777	37683 (12.57)	42955 (14.33)	46255 (15.43)	48640 (16.23)	49098 (16.38)	33878 (11.3)	23746 (7.92)	12713 (4.24)	4809 (1.6)
2005	297246	35031 (11.79)	42935 (14.44)	44612 (15.01)	47130 (15.86)	49039 (16.5)	35960 (12.1)	23940 (8.05)	13537 (4.55)	5062 (1.7)
2006	295263	33458 (11.33)	43085 (14.59)	42264 (14.31)	45953 (15.56)	49345 (16.71)	36916 (12.5)	24571 (8.32)	14337 (4.86)	5334 (1.81)
2007	294004	32018 (10.89)	43590 (14.83)	42923 (14.6)	45547 (15.49)	49521 (16.84)	36272 (12.34)	23884 (8.12)	14860 (5.05)	5389 (1.83)
2008	292896	30568 (10.44)	43552 (14.87)	41869 (14.29)	44192 (15.09)	49971 (17.06)	37401 (12.77)	24388 (8.33)	15328 (5.23)	5627 (1.92)
2009	291464	29091 (9.98)	43118 (14.79)	40439 (13.87)	43731 (15)	49316 (16.92)	39036 (13.39)	24795 (8.51)	15877 (5.45)	6061 (2.08)
2010	292535	27444 (9.38)	42096 (14.39)	36834 (12.59)	42401 (14.49)	48630 (16.62)	42980 (14.69)	28083 (9.6)	17179 (5.87)	6888 (2.35)
2011	284476	26137 (9.19)	39323 (13.82)	35630 (12.52)	40909 (14.38)	47448 (16.68)	43458 (15.28)	27644 (9.72)	17071 (6)	6856 (2.41)
2012	291947	26255 (8.99)	39317 (13.47)	35626 (12.2)	40763 (13.96)	48335 (16.56)	45569 (15.61)	29165 (9.99)	19118 (6.55)	7799 (2.67)
2013	291208	25727 (8.83)	37694 (12.94)	35055 (12.04)	39843 (13.68)	47940 (16.46)	47367 (16.27)	29590 (10.16)	19706 (6.77)	8286 (2.85)
2014	290742	25141 (8.65)	36156 (12.44)	35231 (12.12)	38581 (13.27)	47668 (16.4)	47814 (16.45)	31201 (10.73)	20143 (6.93)	8807 (3.03)

Gwangyang-eup

2002	40412	6506 (16.1)	6041 (14.95)	6632 (16.41)	7393 (18.29)	6145 (15.21)	3212 (7.95)	2614 (6.47)	1337 (3.31)	532 (1.32)
2003	41291	6366 (15.42)	6160 (14.92)	6640 (16.08)	7590 (18.38)	6528 (15.81)	3355 (8.13)	2675 (6.48)	1390 (3.37)	587 (1.42)
2004	42807	6456 (15.08)	6395 (14.94)	6597 (15.41)	8032 (18.76)	6826 (15.95)	3701 (8.65)	2710 (6.33)	1506 (3.52)	584 (1.36)
2005	43434	6161 (14.18)	6589 (15.17)	6606 (15.21)	7975 (18.36)	7109 (16.37)	4044 (9.31)	2711 (6.24)	1626 (3.74)	613 (1.41)
2006	43370	5920 (13.65)	6596 (15.21)	6338 (14.61)	7798 (17.98)	7322 (16.88)	4243 (9.78)	2713 (6.26)	1795 (4.14)	645 (1.49)

2007	44006	5655 (12.85)	6939 (15.77)	6309 (14.34)	7710 (17.52)	7563 (17.19)	4486 (10.19)	2773 (6.3)	1846 (4.19)	725 (1.65)
2008	44610	5517 (12.37)	7022 (15.74)	6216 (13.93)	7508 (16.83)	7836 (17.57)	4828 (10.82)	2911 (6.53)	1981 (4.44)	791 (1.77)
2009	44729	5349 (11.96)	7065 (15.8)	6049 (13.52)	7315 (16.35)	7909 (17.68)	5201 (11.63)	2950 (6.6)	2062 (4.61)	829 (1.85)
2010	44232	4962 (11.22)	6908 (15.62)	5642 (12.76)	7039 (15.91)	7704 (17.42)	5751 (13)	3083 (6.97)	2212 (5)	931 (2.1)
2011	44693	5056 (11.31)	6636 (14.85)	5898 (13.2)	7079 (15.84)	7776 (17.4)	6014 (13.46)	3073 (6.88)	2234 (5)	927 (2.07)
2012	47192	5206 (11.03)	6684 (14.16)	6156 (13.04)	7368 (15.61)	8219 (17.42)	6746 (14.29)	3323 (7.04)	2432 (5.15)	1058 (2.24)
2013	48339	5355 (11.08)	6472 (13.39)	6242 (12.91)	7511 (15.54)	8467 (17.52)	7270 (15.04)	3388 (7.01)	2491 (5.15)	1143 (2.36)
2014	49360	5499 (11.14)	6286 (12.74)	6422 (13.01)	7482 (15.16)	8676 (17.58)	7497 (15.19)	3748 (7.59)	2536 (5.14)	1214 (2.46)
Jungma-dong										
2002	33125	9285 (28.03)	4168 (12.58)	3782 (11.42)	10047 (30.33)	3576 (10.8)	1116 (3.37)	698 (2.11)	317 (0.96)	136 (0.41)
2003	32881	8673 (26.38)	4524 (13.76)	3511 (10.68)	9792 (29.78)	3995 (12.15)	1192 (3.63)	712 (2.17)	330 (1)	152 (0.46)
2004	33943	8460 (24.92)	5018 (14.78)	3515 (10.36)	9849 (29.02)	4494 (13.24)	1347 (3.97)	732 (2.16)	380 (1.12)	148 (0.44)
2005	35708	7959 (22.29)	5844 (16.37)	3782 (10.59)	9818 (27.5)	5253 (14.71)	1671 (4.68)	778 (2.18)	447 (1.25)	156 (0.44)
2006	37889	7881 (20.8)	6578 (17.36)	4056 (10.7)	9813 (25.9)	6096 (16.09)	1941 (5.12)	840 (2.22)	519 (1.37)	165 (0.44)
2007	45189	7653 (16.94)	7390 (16.35)	4866 (10.77)	9876 (21.85)	7276 (16.1)	2997 (6.63)	2962 (6.55)	1756 (3.89)	413 (0.91)
2008	48856	7736 (15.83)	8167 (16.72)	5507 (11.27)	9916 (20.3)	8447 (17.29)	3527 (7.22)	3084 (6.31)	1995 (4.08)	477 (0.98)
2009	51617	7682 (14.88)	8649 (16.76)	5818 (11.27)	10132 (19.63)	9366 (18.15)	4031 (7.81)	3143 (6.09)	2206 (4.27)	590 (1.14)
2010	48688	7696 (15.81)	9202 (18.9)	5531 (11.36)	10102 (20.75)	10085 (20.71)	3803 (7.81)	1262 (2.59)	733 (1.51)	274 (0.56)
2011	49153	7481 (15.22)	9239 (18.8)	5677 (11.55)	9740 (19.82)	10388 (21.13)	4249 (8.64)	1336 (2.72)	751 (1.53)	292 (0.59)

2012	51829	7704 (14.86)	9415 (18.17)	5945 (11.47)	10125 (19.54)	11101 (21.42)	4894 (9.44)	1496 (2.89)	813 (1.57)	336 (0.65)
2013	52297	7567 (14.47)	9186 (17.57)	6044 (11.56)	9759 (18.66)	11391 (21.78)	5534 (10.58)	1620 (3.1)	847 (1.62)	349 (0.67)
2014	53539	7476 (13.96)	9000 (16.81)	6493 (12.13)	9626 (17.98)	11690 (21.83)	6186 (11.55)	1825 (3.41)	871 (1.63)	372 (0.69)
Geumho-domg										
2002	19692	3834 (19.47)	4334 (22.01)	1560 (7.92)	4490 (22.8)	4200 (21.33)	893 (4.53)	133 (0.68)	170 (0.86)	78 (0.4)
2003	19097	3375 (17.67)	4345 (22.75)	1544 (8.09)	4146 (21.71)	4199 (21.99)	1087 (5.69)	150 (0.79)	162 (0.85)	89 (0.47)
2004	18731	2891 (15.43)	4467 (23.85)	1615 (8.62)	3728 (19.9)	4195 (22.4)	1384 (7.39)	172 (0.92)	182 (0.97)	97 (0.52)
2005	18114	2429 (13.41)	4535 (25.04)	1608 (8.88)	3199 (17.66)	4176 (23.05)	1682 (9.29)	193 (1.07)	193 (1.07)	99 (0.55)
2006	17372	2002 (11.52)	4521 (26.02)	1616 (9.3)	2695 (15.51)	4163 (23.96)	1878 (10.81)	211 (1.21)	191 (1.1)	95 (0.55)
2007	21358	1566 (7.33)	4660 (21.82)	2521 (11.8)	2289 (10.72)	4495 (21.05)	2290 (10.72)	1471 (6.89)	1604 (7.51)	462 (2.16)
2008	20677	1306 (6.32)	4608 (22.29)	2482 (12)	1821 (8.81)	4607 (22.28)	2376 (11.49)	1358 (6.57)	1626 (7.86)	493 (2.38)
2009	20226	1098 (5.43)	4537 (22.43)	2571 (12.71)	1580 (7.81)	4591 (22.7)	2450 (12.11)	1209 (5.98)	1650 (8.16)	540 (2.67)
2010	16048	937 (5.84)	4331 (26.99)	1970 (12.28)	1305 (8.13)	4309 (26.85)	2534 (15.79)	345 (2.15)	186 (1.16)	131 (0.82)
2011	15543	864 (5.56)	4000 (25.74)	2152 (13.85)	1210 (7.78)	3999 (25.73)	2605 (16.76)	403 (2.59)	181 (1.16)	129 (0.83)
2012	15467	895 (5.79)	3707 (23.97)	2277 (14.72)	1213 (7.84)	3821 (24.7)	2705 (17.49)	540 (3.49)	181 (1.17)	128 (0.83)
2013	14929	936 (6.27)	3356 (22.48)	2239 (15)	1219 (8.17)	3513 (23.53)	2696 (18.06)	665 (4.45)	173 (1.16)	132 (0.88)
2014	14495	994 (6.86)	2945 (20.32)	2420 (16.7)	1256 (8.67)	3097 (21.37)	2654 (18.31)	828 (5.71)	178 (1.23)	123 (0.85)

Statistical analysis

We performed an interrupted time-series analysis to test whether the operation of the ferronickel factory changed the incidence levels of asthma, allergic rhinitis, and dermatitis among Gwangyang and Yeosu City residents (Bernal et al. 2016). We set November 2008, just after the opening of the factory, as the advent of the effect of the ferronickel manufacturing factory operation and ferronickel slag on the residents. We hypothesized an abrupt increase in the incidence of irritant or allergic disease after the opening of the ferronickel factory based on the results of previous studies suggesting that the exposure to heavy metal dust induces irritant or allergic symptoms within a short time (Otani et al. 2012). Therefore, the abrupt level change of each disease incidence after the opening of the ferronickel factory was assessed with a segmented quasi-Poisson regression model. We assumed the parallel trend between Gwangyang and Yeosu City's disease-specific incidence rates for the period before the ferronickel factory operation by visually comparing the monthly time-series patterns (Figure 5 and Figure 6). To account for over-dispersion and seasonality issues, we used the quasi-Poisson model with harmonic terms for months in our model (Bernal et al. 2016). We used following equation model in our main analysis.

$$\log [\mu_t] = \beta_0 + \beta_1 I_t + \beta_2 T_t + \beta_3 M$$

The age-standardized disease specific monthly incidence rate was assumed to follow a quasi-Poisson distribution with the mean μ_t with t indexing the month, I_t as an indicator variable for operation of the factory (I_t=1: after the factory operation, I_t=0:

before the factory operation), T_t as the time elapsed since the start of the study (from Jan 2004, in month unit), and *M* as the harmonic terms with 2 pairs of sin and cosine for 12 months to adjust seasonality. We exponentiated β_1 to estimate the abrupt changes in the monthly incidence patterns of asthma, allergic rhinitis, and dermatitis of residents before (January 2004-October 2008) and after (November 2008-December 2014) the operation of the ferronickel factory.

In a time-series analysis, the basic regression assumption can be violated by residual autocorrelation of time-series outcomes. Therefore, we evaluated the residual autocorrelation with the Breusch-Godfrey test for each time-series, and if the residual autocorrelation was present ($p<0.05$), we used robust standard errors by using a sandwich estimator to report more conservative estimates as suggested in previous studies (Andrews 1991; Humphreys et al. 2017).

To compare differences between relative risk estimates of step change after the operation of the ferronickel factory between Gwangyang and Yeosu City, we used following equation (Altman and Bland 2003).

$$(\beta_1 - \beta_2) / \sqrt{SE_1^2 + SE_2^2}$$

Where β_1 and β_2 are step change estimates for Gwangyang and Yeosu cities at November 2008, and SE_1 and SE_2 are their respective standard errors. An absolute value larger than 1.96 indicates a statistically significant difference at the $\alpha = 0.05$ level. We conducted stratified analysis on different age groups (0-9, 10-29, 30-59, and 60-) and different sub-regions of Gwangyang City residents (Jungma-dong,

Geumho-dong, and Gwangyang-eup).

For the sensitivity analysis, we conducted our main analysis by combining the Gwangyang and Yeosu City's monthly incidence rate in the single model. We weighted Gwangyang City's disease specific monthly incidence rate with control city, Yeosu City's rate using the methods suggested in recent paper (Yorifuji and Kashima 2016).

Weighted disease incidence rate of Gwangyang City =

Monthly disease incidence rate $_{Gwangyang\ City}$ X

Disease incidence rate $_{Yeosu\ City,Jan\ 2004}$ / Monthly disease incidence rate $_{Yeosu\ City}$

With this methods, we may enable to estimate the effects of ferronickel factory operation after accounting for potential effects of confounders which might occurred during the timing of the factory operation in both Gwangyang and Yeosu City (Lopez Bernal et al. 2018).

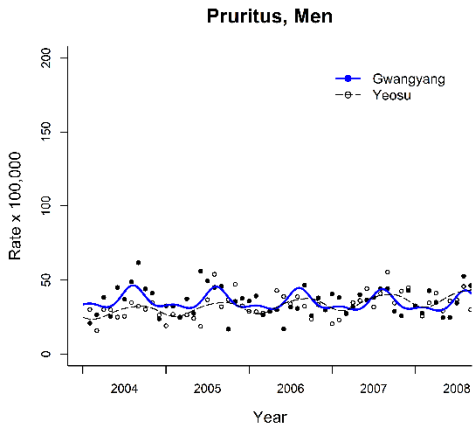
To confirm our findings from interrupted time-series analysis, we conducted additional difference-in-difference analysis. The difference-in-difference analysis compares the changes in outcome over time between intervention and reference population (Gertler et al. 2016; Hanchate et al. 2015). We estimated the relative change in disease incidence rate associated with ferronickel factory operation of Gwangyang City residents as the difference of following two differences: First difference, the difference in the before-and-after disease incidence rate for the Gwangyang City residents; Second difference, the difference in the before-and-after

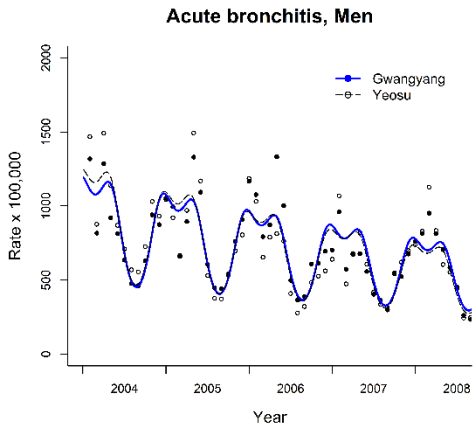
disease incidence rate for the Yeosu City residents. The first difference controls for the factors which are constant over time by comparing disease incidence in same Gwangyang City population. In addition, by subtracting first difference with second difference, we controlled time varying factors by assuming the changes in disease incidence rate of Yeosu City residents represents the changes in disease incidence rate that would be experienced by the Gwanyang City residents in the absence of ferronickel factory operation. We divided study period into 4 years before [2004.11-2006.10 (reference period), 2006.11-2008.10] and 6 years after (2008.11-2010.10, 2010.11-2012.10, 2012.12-2014.10) the ferronickel factory operation and estimated how monthly disease incidence rate of Gwangyang City residents changed relative to Yeosu City residents. Detailed difference-in-difference analysis equation are as follows.

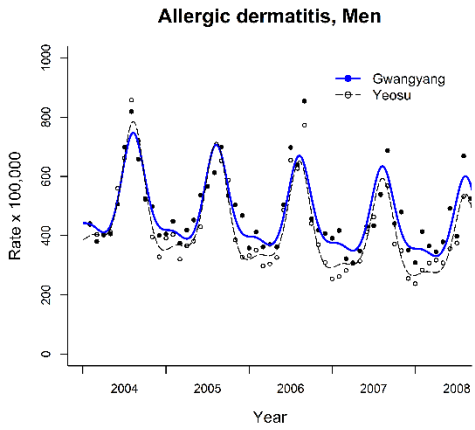
$$\log[\mu_t] = \beta_0 + \beta_1 R + \beta_2 T_t + \beta_3 P_1 + \beta_4 P_2 + \beta_5 P_3 + \beta_6 P_4 + \beta_7 R{*}P_1 + \beta_8 R{*}P_2 + \beta_9 R{*}P_3 + \beta_{10} R{*}P_4 + \varepsilon$$

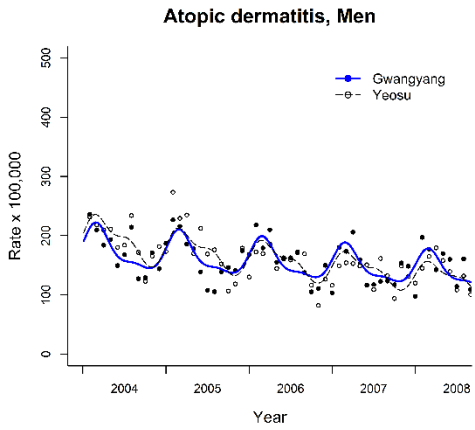
R as an indicator variable for region (R=1 Gwangyang City, R=0 Yeosu City), T_t as the time elapsed since the start of the study (in month unit), P_x as an indicator variable for study period after the ferronickel factory operation (P_1= 2006.11-2008.10; P_2= 2008.11-2010.10; P_3= 2010.11-2012.10; P_4= 2012.11-2014.10), and $R{*}P_x$ as an interaction term between region and period indicators. We exponentiated β_7 to β_{10} to estimate difference-in-difference estimates for each time period before (2006.11-2008.10) and after (2008.11-2010.10, 2010.11-2012.10, 2012.12-2014.10) the ferronickel factory operation. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA)

and R statistical software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria) were used in our analysis. From R statistical software, the harmonic function (to utilize Fourier terms to adjust seasonality) from tsModel package, dwtest function (to evaluate autocorrelation) from lmtest package, and vovHC (to generate robust standard error) function from sandwich package were used in our analysis.


Pruritus, Men
Gwangyang
Yeosu
Rate x 100,000
0
50
100
150
200
2004
2005
2006
2007
2008
Year


Acute bronchitis, Men
Gwangyang
Yeosu
Rate x 100,000
0
500
1000
1500
2000
2004
2005
2006
2007
2008
Year


Allergic dermatitis, Men
Gwangyang
Yeosu
Rate x 100,000
0
200
400
600
800
1000
2004
2005
2006
2007
2008
Year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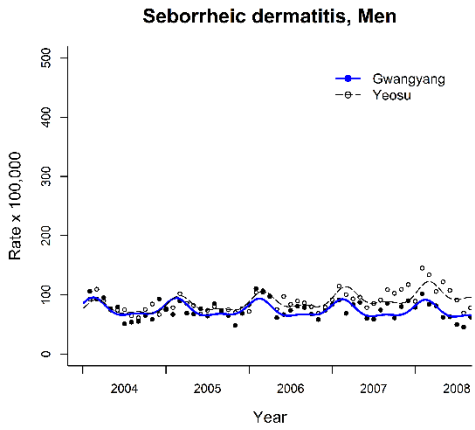
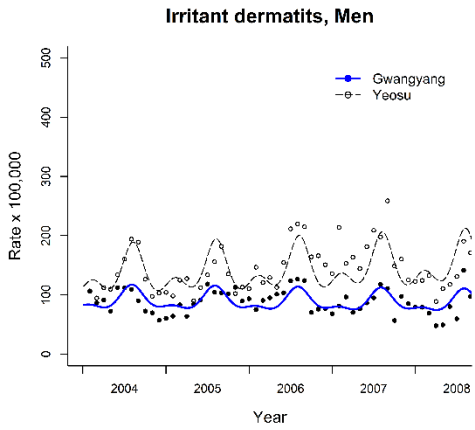
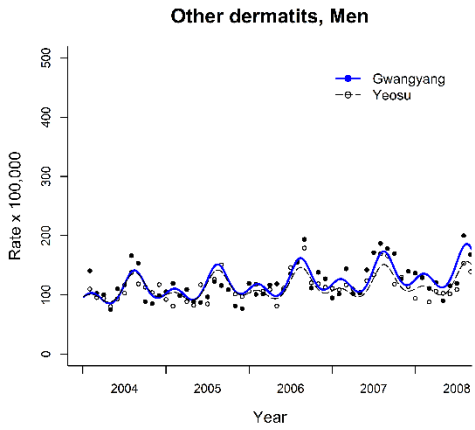
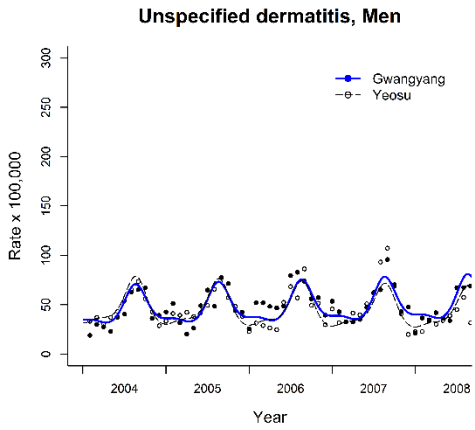
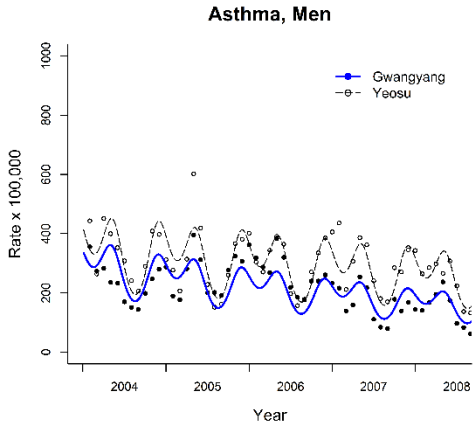
Gwangyang
Yeosu
Rate x 100,000
0
100
200
300
400
500
2004
2005
2006
2007
2008
Year

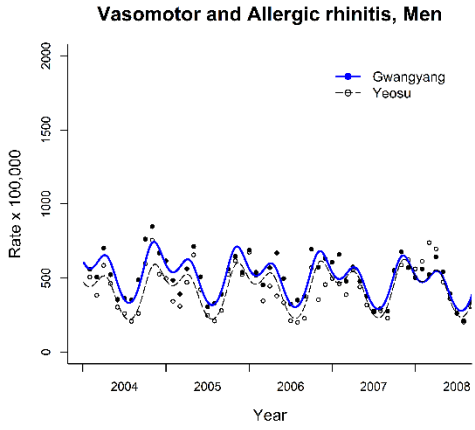

Seborrheic dermatitis, Men
Gwangyang
Yeosu
Rate x 100,000
0
100
200
300
400
500
2004
2005
2006
2007
2008
Year

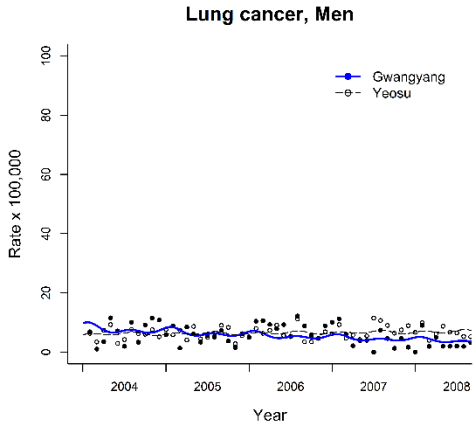

Irritant dermatits, Men
Gwangyang
Yeosu
Rate x 100,000
0
100
200
300
400
500
2004
2005
2006
2007
2008
Year

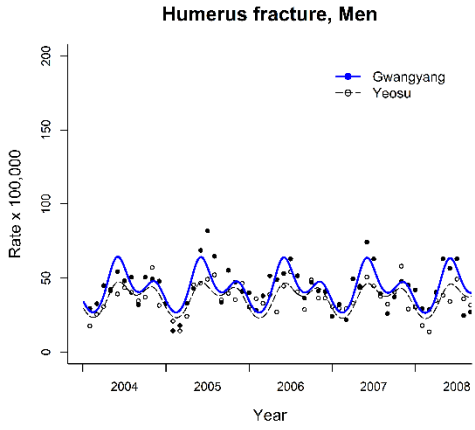

Other dermatits, Men
Gwangyang
Yeosu
Rate x 100,000
0
100
200
300
400
500
2004
2005
2006
2007
2008
Year


Unspecified dermatitis, Men
Gwangyang
Yeosu
Rate x 100,000
0
50
100
150
200
250
300
2004
2005
2006
2007
2008
Year


Asthma, Men
Gwangyang
Yeosu
Rate x 100,000
0
200
400
600
800
1000
2004
2005
2006
2007
2008
Year


Vasomotor and Allergic rhinitis, Men
Gwangyang
Yeosu
Rate x 100,000
0
500
1000
1500
2000
2004
2005
2006
2007
2008
Year


Lung cancer, Men
Gwangyang
Yeosu
Rate x 100,000
0
20
40
60
80
100
2004
2005
2006
2007
2008
Year


Humerus fracture, Men
Gwangyang
Yeosu
Rate x 100,000
0
50
100
150
200
2004
2005
2006
2007
2008
Year

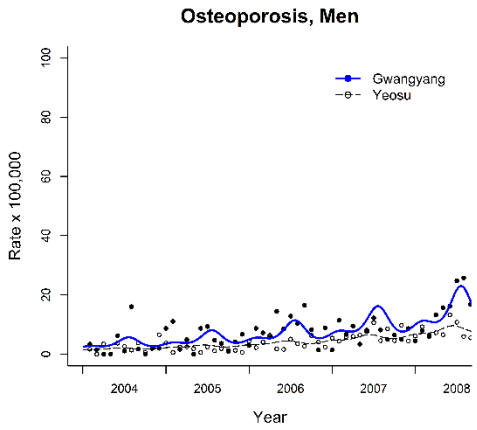
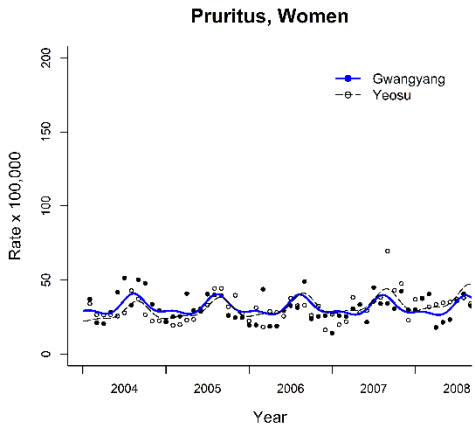
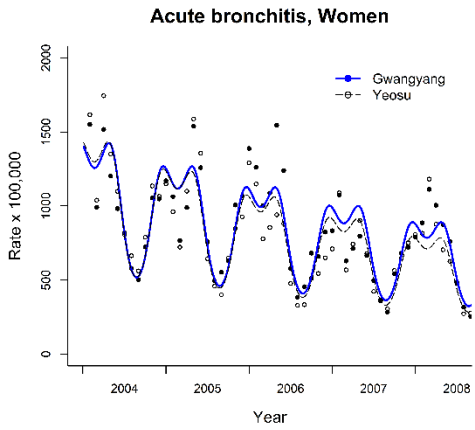


Figure 5. The monthly disease incidence time-series patterns (men) of Gwangyang (black circle) and Yeosu City (white circle) before the ferronickel factory operation (2004.01-2008.10). The curved line (blue: Gwangyang City; black: Yeosu City) represents seasonality adjusted regression model.


Pruritus, Women
Gwangyang
Yeosu
Rate x 100,000
0
50
100
150
200
2004
2005
2006
2007
2008
Year


Acute bronchitis, Women
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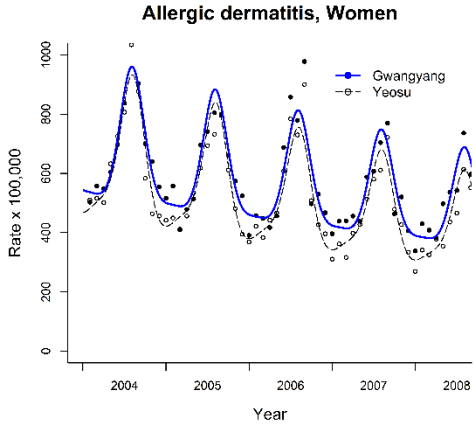
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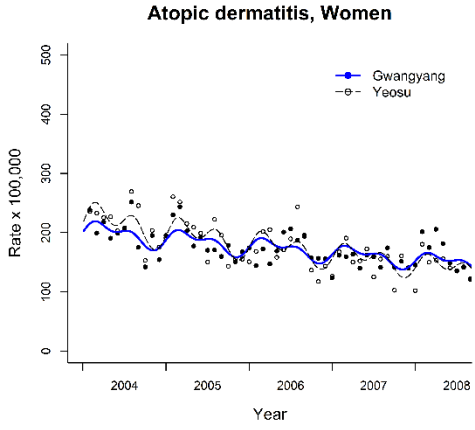
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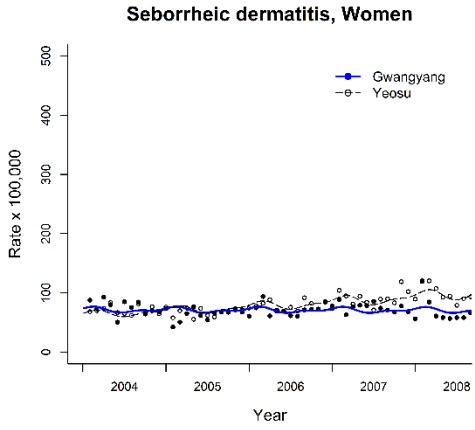
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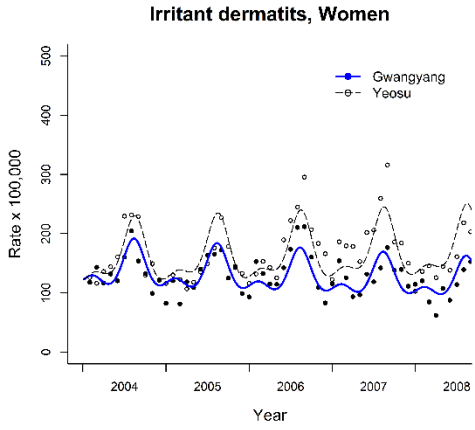
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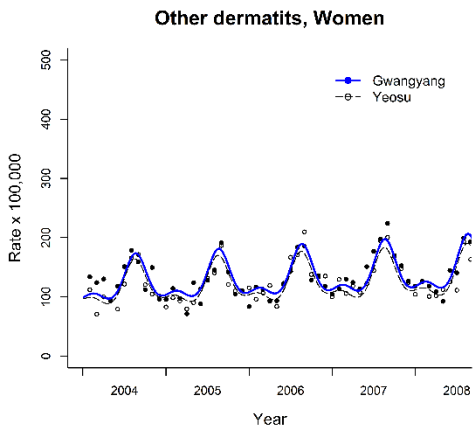
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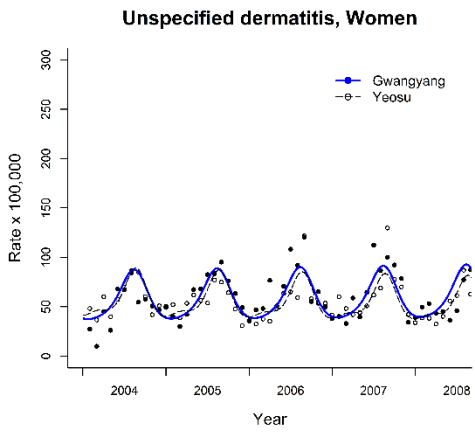
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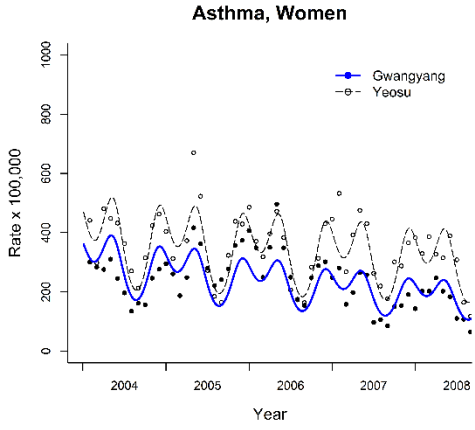
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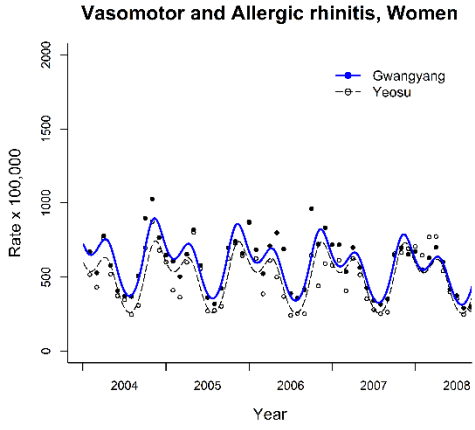
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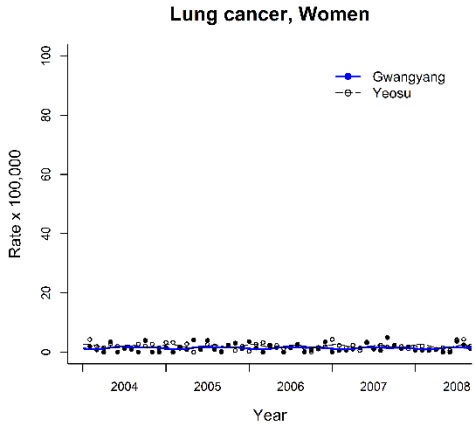
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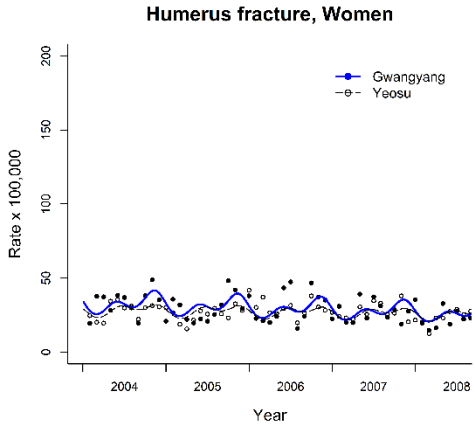
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Yeosu
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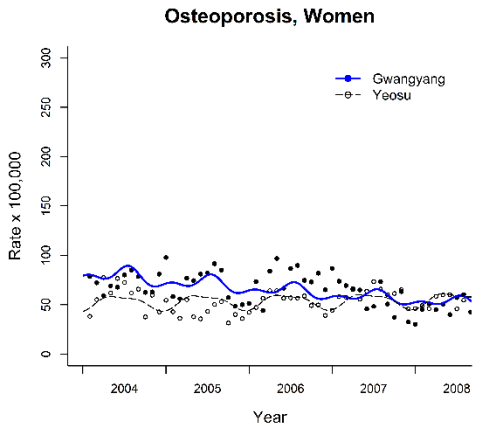


Figure 6. The monthly disease incidence time-series patterns (women) of Gwangyang (black circle) and Yeosu City (white circle) before the ferronickel factory operation (2004.01-2008.10). The curved line (blue: Gwangyang City; black: Yeosu City) represents seasonality adjusted regression model.

Results

We estimated the abrupt changes in the monthly incidence patterns of asthma, allergic rhinitis, and dermatitis of residents before (January 2004-October 2008) and after (November 2008-December 2014) the operation of the ferronickel factory (Table 5, Figure 7). In Gwangyang City men, we found an abrupt increase in the monthly incidence rates of pruritus [relative risk (RR), (95% confidence interval (CI)): 1.49 (1.12-1.99)], atopic dermatitis [RR (95% CI): 1.17 (1.04-1.31)], unspecified contact dermatitis [RR (95% CI): 1.75 (1.17-2.60)], asthma [RR (95% CI): 1.21 (1.00-1.46)], and vasomotor and allergic rhinitis [RR (95% CI): 1.23 (1.08-1.39)] after the operation of the ferronickel factory. In Gwangyang City women, an increase in the monthly incidence rates of pruritus [RR (95% CI): 1.95 (1.51-2.52)], atopic dermatitis [RR (95% CI): 1.17 (1.06-1.30)], unspecified contact dermatitis [RR (95% CI): 1.65 (1.04-2.60)], asthma [RR (95% CI): 1.25 (1.03-1.51)], and vasomotor and allergic rhinitis [RR (95% CI): 1.17 (1.04-1.31)] was observed after the operation of the ferronickel factory. In particular, there was an abrupt short-term increase in the monthly incidence of unspecified contact dermatitis in the summer period of 2009 in both men and women (Figure 7). Detailed age-standardized monthly disease incidence rate patterns by men and women are summarized at Figure 8 and Figure 9.

We compared the analysis results of Gwangyang City residents with the results of the comparison city, Yeosu. All the disease outcomes except pruritus and osteoporosis showed a null association between the ferronickel factory operation and the changes

in disease incidence of Yeosu City. By comparing step change RR estimates between Gwangyang and Yeosu city, a significant difference in ferronickel factory operation effects on unspecified contact dermatitis and vasomotor and allergic rhinitis in men, and pruritus, unspecified contact dermatitis, and vasomotor and allergic rhinitis in women were noticed (Table 5).

Sensitivity analysis using weighting methods also showed similar results to our main analysis (Table 6). Weighted monthly disease incidence rate of Gwangyang City men showed abrupt increase in atopic dermatitis [RR (95% CI): 1.17 (1.00-1.36)], unspecified contact dermatitis [RR (95% CI): 2.28 (1.37-3.79)], and vasomotor and allergic rhinitis [RR (95% CI): 1.27 (1.13-1.43)]. Weighted monthly disease incidence rate of Gwangyang City women showed abrupt increase in pruritus [RR (95% CI): 1.46 (1.14-1.88)], unspecified contact dermatitis [RR (95% CI): 2.47 (1.32-4.63)], and vasomotor and allergic rhinitis [RR (95% CI): 1.15 (1.04-1.28)].

Additional difference-in-difference analysis showed similar results to our main analysis (Table 7 and 8). By comparing 2008.11-2010.10 period to the reference period before the ferronickel factory operation (2004.11-2006.10), significant increase in monthly incidence rates of atopic dermatitis and unspecified contact dermatitis of Gwangyang City were observed even after accounting for the changes of Yeosu City [RR (95% CI), atopic dermatitis, men: 1.19 (1.02-1.38), women: 1.21 (1.07-1.36); unspecified contact dermatitis, men: 1.71 (1.23-2.40), women: 1.54 (1.07-2.21)]. By comparing 2010.11-2012.10 period to reference period, significant increase in monthly incidence rates of pruritus and other dermatitis in Gwangyang

City were observed even after accounting for the changes of Yeosu City [RR (95% CI), pruritus, men: 1.64 (1.24-2.17), women: 1.44 (1.09-1.91); other dermatitis, men: 1.27 (1.08-1.50), women: 1.32 (1.08-1.61)]. There was no significant differences between Gwangyang and Yeosu City before (2004.11-2006.10 and 2006.11-2008.10) the ferronickel factory operation.

Stratified analysis of the different age groups of Gwangyang City residents showed that the impact of ferronickel factory operation on the monthly incidence patterns of irritant or allergic disease was greater among children aged between 0 to 9 (Table 9). However, the abrupt short-term increase in the incidence of unspecified contact dermatitis in the summer of 2009 was only observed in residents aged 10 years or older.

The analysis for the sub-regions of Gwangyang City showed that the magnitude of increase in monthly asthma, allergic rhinitis, and dermatitis incidence were greater in sub-regions near the factory site (<10km, Jungma-dong, Geumho-dong) compared to the farther located sub-region (>15km, Gwangyang-eup) (Table 10, Figure 10). Jungma-dong, the highest populated sub-region near the factory site, showed greater increase in the disease incidence compared to the other sub-regions. In particular, the abrupt short-term increase of unspecified contact dermatitis incidence in the summer of 2009 was only observed in sub-regions near the ferronickel factory (Figure 10).

Table 5. The association between the operation of the ferronickel factory (2008.11-) and the incidence of allergic and irritant disease in Gwangyang and Yeosu City.

Disease	Mean number of monthly incidence cases		Mean monthly incidence rate[a] x 100,000		Relative risk (95% CI)	Test of interaction
	Before (2004.01-2008.10)	After (2008.11-2014.12)	Before (2004.01-2008.10)	After (2008.11-2014.12)	Step change	(Gwangyang vs Yeosu)
Men						
Pruritus						
Gwangyang	26.53	39.58	35.70	63.77	1.49 (1.12, 1.99)[b]	0.17
Yeosu	48.45	68.95	32.94	46.88	1.19 (1.03, 1.39)[b]	
Acute bronchitis						
Gwangyang	483.97	369.35	719.83	563.19	1.05 (0.89, 1.22)[b]	0.96
Yeosu	1007.93	589.22	714.87	479.04	1.04 (0.86, 1.25)[b]	
Allergic dermatitis						
Gwangyang	329.57	267.31	474.54	380.84	1.04 (0.95, 1.13)	0.70
Yeosu	621.95	421.16	426.85	321.20	1.06 (0.98, 1.16)[b]	
Atopic dermatitis						
Gwangyang	86.57	62.34	156.85	122.51	1.17 (1.04, 1.31)	0.16
Yeosu	154.33	93.65	158.77	117.96	1.05 (0.95, 1.15)[b]	
Seborrheic dermatitis						
Gwangyang	55.43	59.93	74.74	77.62	1.04 (0.94, 1.15)[b]	0.38

Yeosu	141.90	142.59	88.79	94.31	0.97 (0.86, 1.09)[b]	
Irritant contact dermatitis						
Gwangyang	59.66	54.53	89.56	84.50	0.91 (0.79, 1.05)[b]	0.19
Yeosu	212.86	163.16	143.09	127.89	0.80 (0.72, 0.90)[b]	
Other dermatitis						
Gwangyang	78.66	93.28	123.08	162.01	0.90 (0.82, 1.00)[b]	0.85
Yeosu	164.12	174.01	113.90	134.96	0.91 (0.83, 1.00)[b]	
Unspecified contact dermatitis						
Gwangyang	35.22	36.89	48.74	47.85	1.75 (1.17, 2.60)[b]	<0.01
Yeosu	66.79	58.85	45.57	40.97	0.85 (0.70, 1.03)[b]	
Asthma						
Gwangyang	125.22	105.80	215.33	183.91	1.21 (1.00, 1.46)[b]	0.40
Yeosu	363.67	230.39	299.56	226.09	1.08 (0.91, 1.28)[b]	
Vasomotor and allergic rhinitis						
Gwangyang	342.66	308.80	507.54	490.56	1.23 (1.08, 1.39)[b]	0.02
Yeosu	594.83	446.51	435.12	374.06	0.95 (0.80, 1.12)[b]	
Lung cancer						
Gwangyang	3.76	4.73	5.62	5.23	1.00 (0.67, 1.49)	0.59
Yeosu	11.26	12.34	6.56	5.64	0.89 (0.73, 1.08)	
Fracture of forearm						

Gwangyang	27.88	24.00	43.94	35.17	0.86 (0.73, 1.00)	0.69
Yeosu	46.38	39.01	36.90	32.55	0.89 (0.78, 1.01)	
Osteoporosis						
Gwangyang	5.78	9.91	7.93	11.2	1.30 (0.82, 2.08)	0.81
Yeosu	7.55	19.03	4.38	8.46	1.39 (1.01, 1.92)	
Women						
Pruritus						
Gwangyang	23.81	44.72	31.33	68.54	1.95 (1.51, 2.52)[b]	<0.01
Yeosu	50.41	86.19	31.68	56.16	1.28 (1.13, 1.45)[b]	
Acute bronchitis						
Gwangyang	545.00	369.09	838.21	602.20	1.01 (0.86, 1.18)[b]	0.56
Yeosu	1098.86	561.47	794.00	485.48	1.08 (0.91, 1.28)[b]	
Allergic dermatitis						
Gwangyang	390.43	286.61	578.04	425.77	1.03 (0.95, 1.12)	0.58
Yeosu	766.48	482.72	521.28	371.56	1.07 (0.98, 1.16)[b]	
Atopic dermatitis						
Gwangyang	91.47	66.34	172.87	131.21	1.17 (1.06, 1.30)	0.37
Yeosu	164.29	100.18	175.16	126.42	1.09 (0.99, 1.21)[b]	
Seborrheic dermatitis						

Gwangyang	49.97	55.12	71.00	79.29	1.07 (0.95, 1.21)	0.72
Yeosu	119.34	131.09	80.54	96.20	1.11 (0.97, 1.26)[b]	
Irritant contact dermatitis						
Gwangyang	86.84	79.91	129.16	121.37	0.91 (0.78, 1.05)[b]	0.87
Yeosu	253.28	201.12	167.01	155.98	0.89 (0.81, 0.98)[b]	
Other dermatitis						
Gwangyang	83.90	106.74	133.67	181.69	0.97 (0.87, 1.07)[b]	0.50
Yeosu	176.79	195.69	124.59	152.52	0.92 (0.84, 1.01)[b]	
Unspecified contact dermatitis						
Gwangyang	43.28	50.85	59.92	64.17	1.65 (1.04, 2.60)[b]	0.01
Yeosu	83.64	83.88	56.27	56.86	0.85 (0.71, 1.01)[b]	
Asthma						
Gwangyang	143.03	130.76	235.44	212.16	1.25 (1.03, 1.51)[b]	0.37
Yeosu	441.83	276.93	341.76	248.37	1.11 (0.92, 1.32)[b]	
Vasomotor and allergic rhinitis						
Gwangyang	383.34	319.84	590.57	535.58	1.17 (1.04, 1.31)	0.05
Yeosu	702.07	487.26	509.21	409.74	0.96 (0.82, 1.12)[b]	
Lung cancer						
Gwangyang	1.38	2.19	1.42	1.92	0.76 (0.43, 1.34)	0.20
Yeosu	4.52	4.86	1.94	1.76	1.17 (0.83, 1.64)	

Fracture of forearm						
Gwangyang	19.78	20.32	29.29	25.48	1.02 (0.82, 1.28)	0.53
Yeosu	43.50	43.36	27.25	24.42	0.95 (0.82, 1.10)	
Osteoporosis						
Gwangyang	56.59	50.73	64.99	50.03	1.04 (0.89, 1.21)	0.75
Yeosu	119.07	131.32	53.72	51.18	1.07 (0.97, 1.19)	

[a] Age standardised according to WHO standard population
[b] Breusch-Godfrey test revealed serial autocorrelation. Therfore, robust standard errors are used to calculate 95% confidence intervals

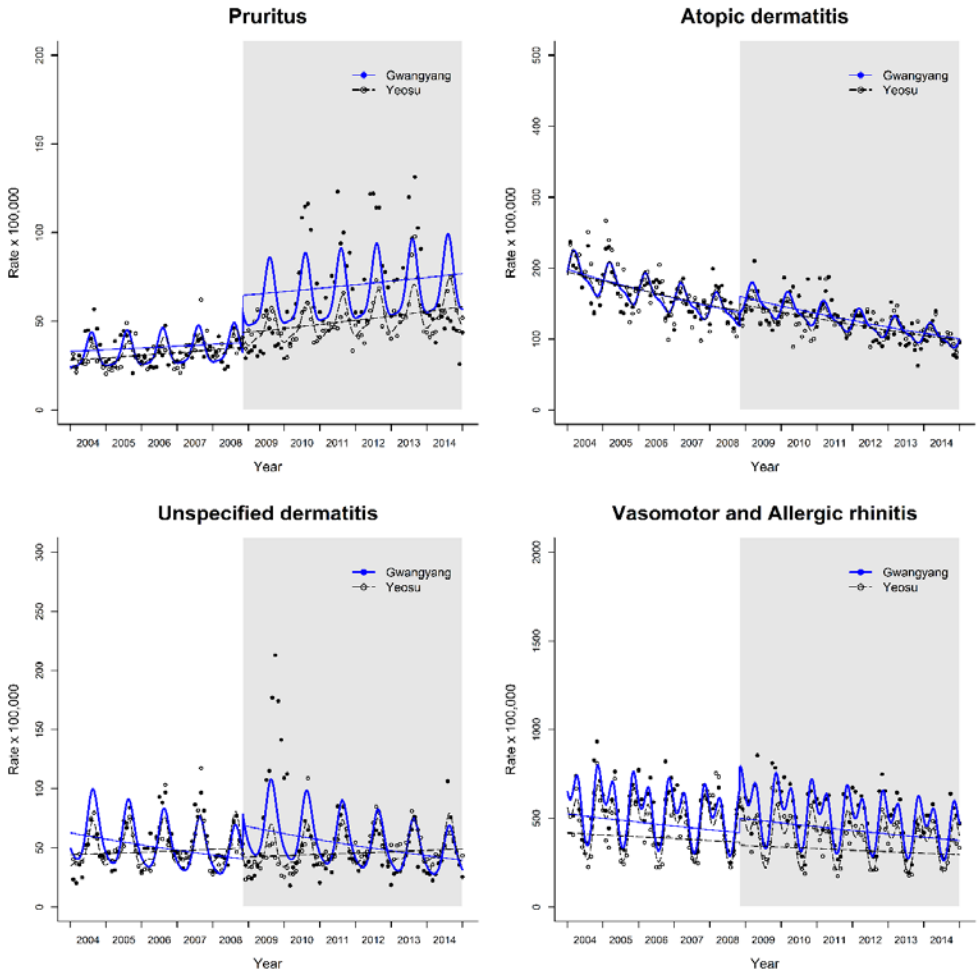
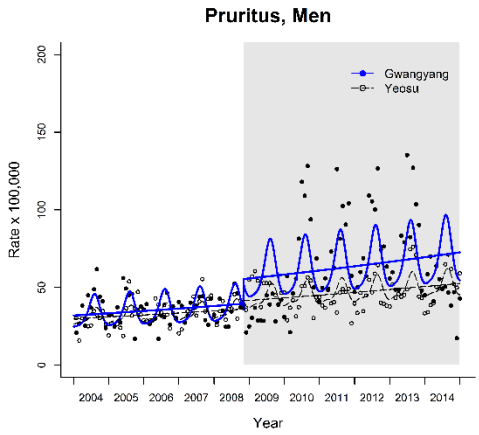


Figure 7. The association between the operation of the ferronickel factory (2008.11-) and the monthly incidence of allergic and irritant disease in Gwangyang and Yeosu City. Data points represent the monthly incidence rates of each disease in Gwangyang and the comparison city, Yeosu. Straight lines represent fitted estimates using a linear step change model, and the curved lines represent the seasonality adjusted model. The white and gray backgrounds represent the periods before (2004.01-2008.10) and after (2008.11-2014.12) the operation of the ferronickel factory.


Pruritus, Men
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Yeosu
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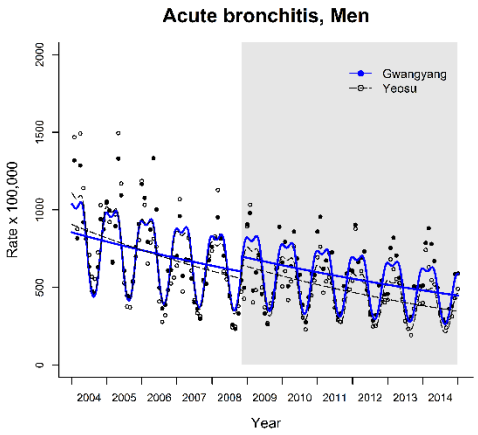
Year


Acute bronchitis, Men
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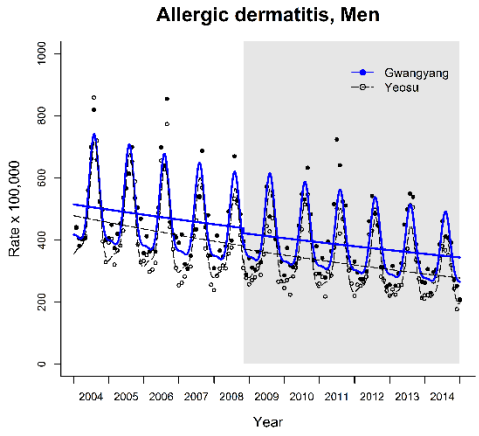
Yeosu
Rate x 100,000
Year


Allergic dermatitis, Men
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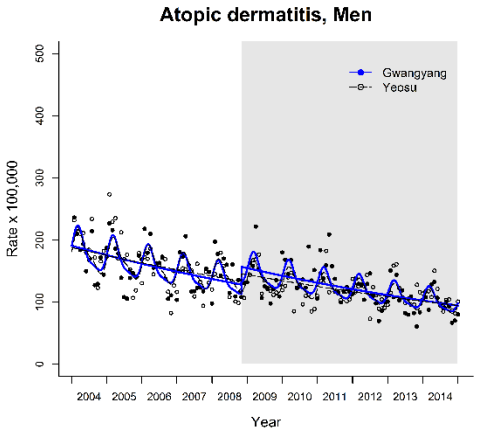
Year


Atopic dermatitis, Men
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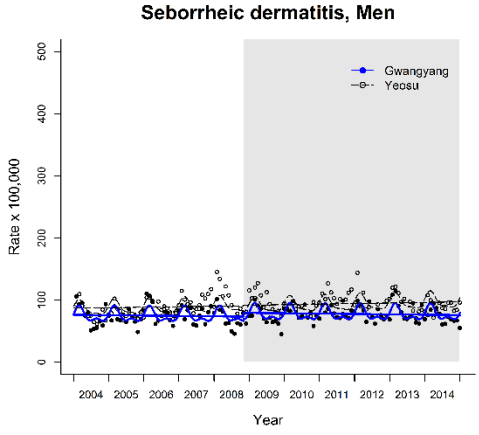
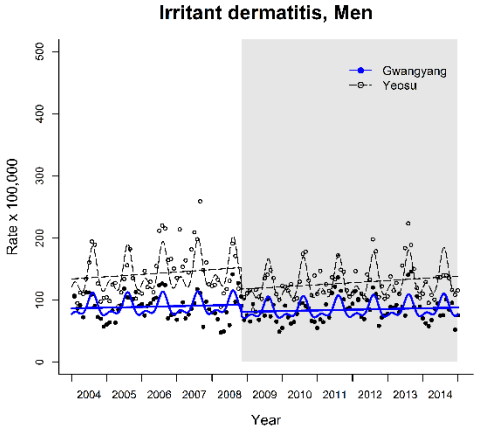
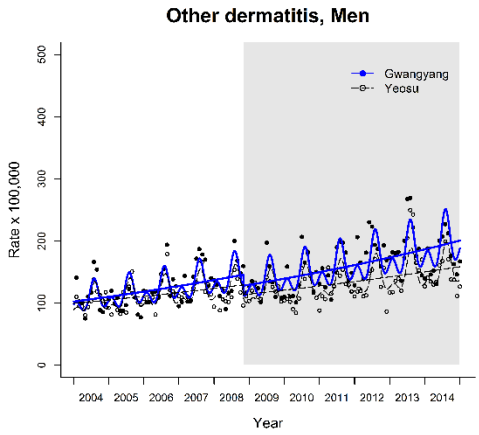
Rate x 100,000
Year


Seborrheic dermatitis, Men
Gwangyang
Yeosu
Rate x 100,000
Year


Irritant dermatitis, Men
Gwangyang
Yeosu
Rate x 100,000
Year


Other dermatitis, Men
Gwangyang
Yeosu
Rate x 100,000
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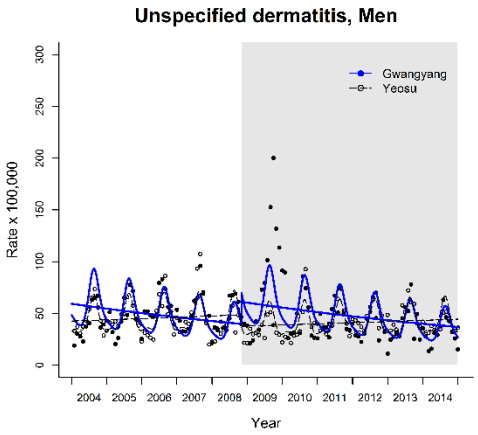
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year


Unspecified dermatitis, Men
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Rate x 100,000
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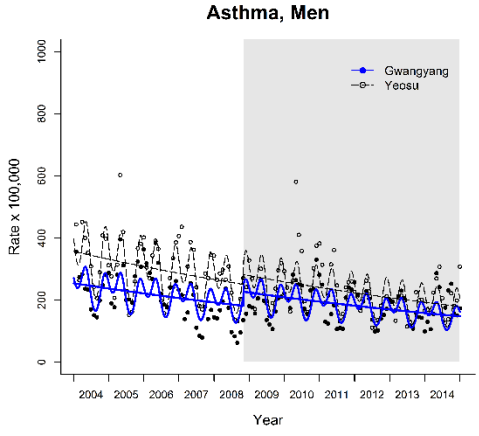
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year


Asthma, Men
Gwangyang
Yeosu
Rate x 100,000
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400
600
800
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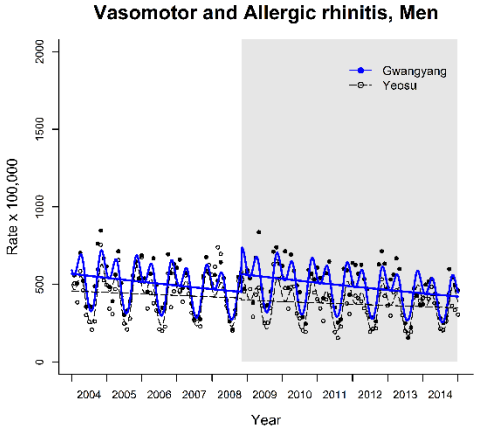
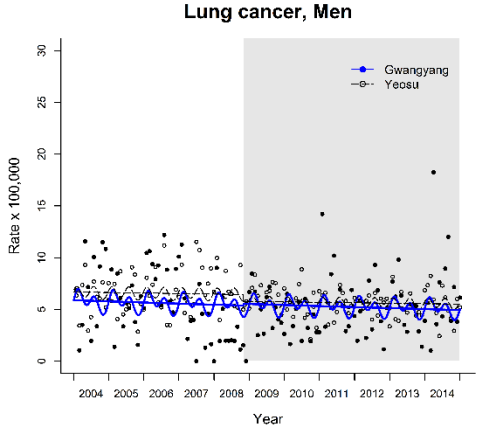
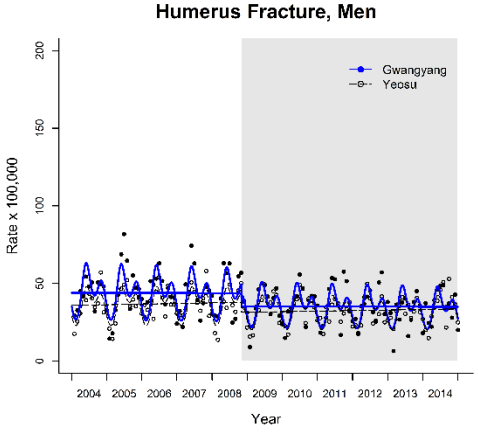
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year


Vasomotor and Allergic rhinitis, Men
Gwangyang
Yeosu
Rate x 100,000
0
500
1000
1500
2000
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year


Lung cancer, Men
Gwangyang
Yeosu
Rate x 100,000
0
5
10
15
20
25
30
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year


Humerus Fracture, Men
Gwangyang
Yeosu
Rate x 100,000
0
50
100
150
200
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year

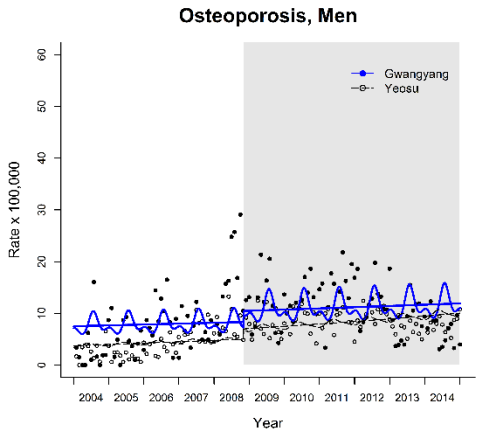
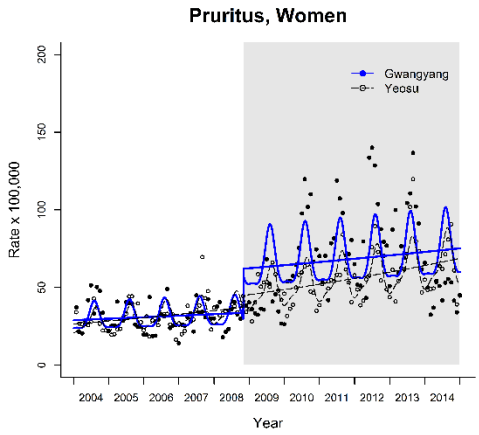
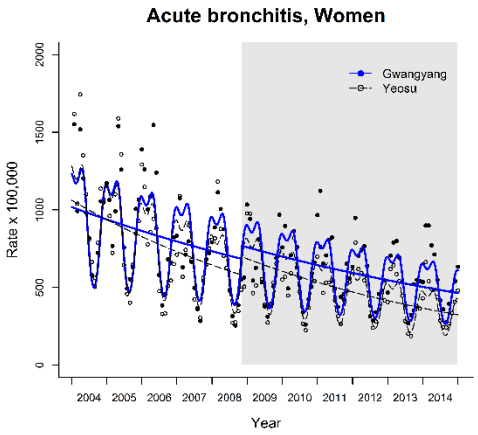
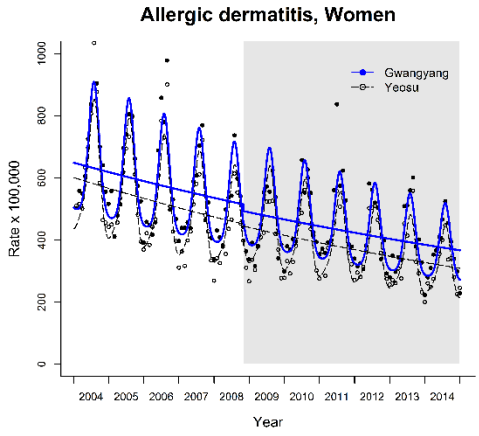
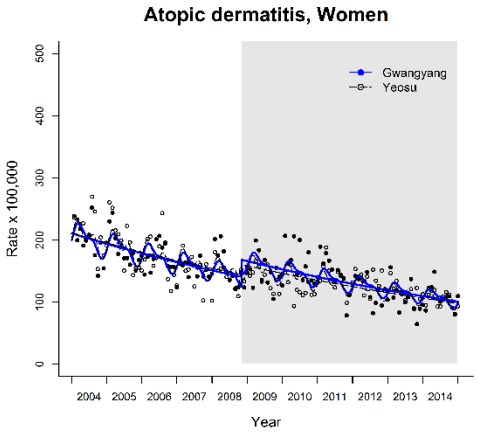


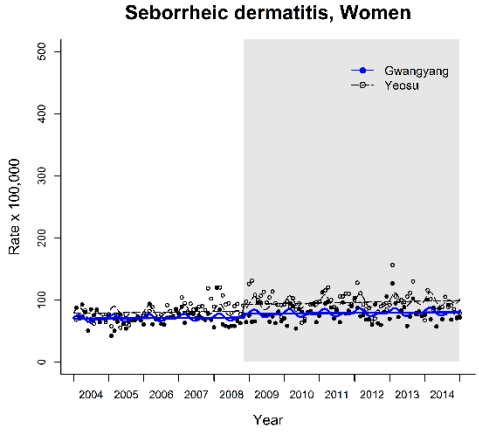
Figure 8. The association between the operation of the ferronickel factory (2008.11-) and the incidence of allergic and irritant disease in Gwangyang and Yeosu City men. Data points represent the monthly incidence rates of each disease in Gwangyang and the comparison city, Yeosu. Straight lines represent fitted estimates using a linear step change model, and the curved lines represent the seasonality adjusted model. The white and gray backgrounds represent the periods before (2004.01-2008.10) and after (2008.11-2014.12) the operation of the ferronickel factory.

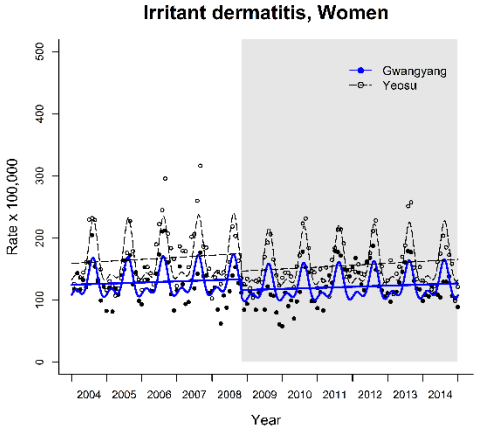

Pruritus, Women
Gwangyang
Yeosu
Rate x 100,000
Year

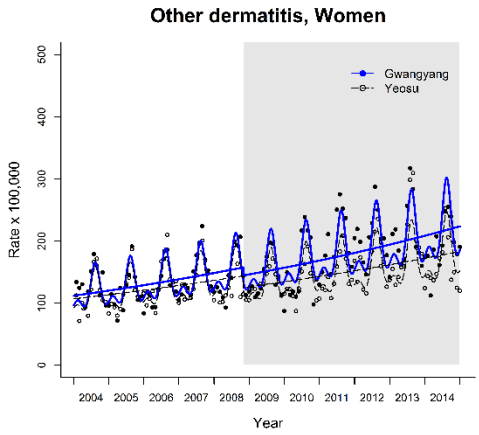

Acute bronchitis, Women
Gwangyang
Yeosu
Rate x 100,000
Year

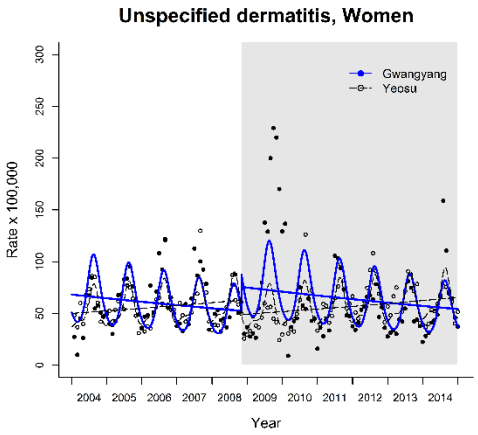

Allergic dermatitis, Women
Gwangyang
Yeosu
Rate x 100,000
Year

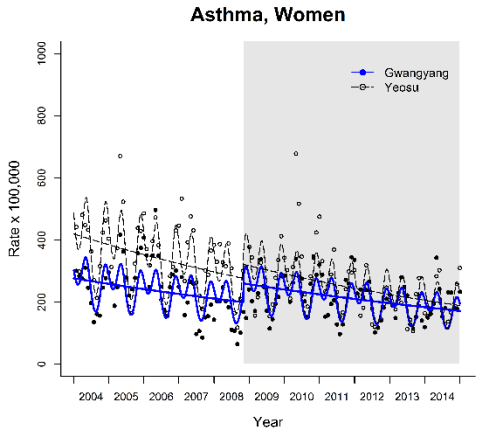

Atopic dermatitis, Women
Gwangyang
Yeosu
Rate x 100,000
Year

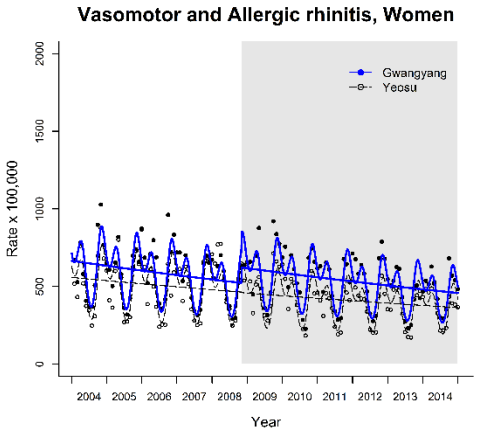

Seborrheic dermatitis, Women
Gwangyang
Yeosu
Rate x 100,000
Year

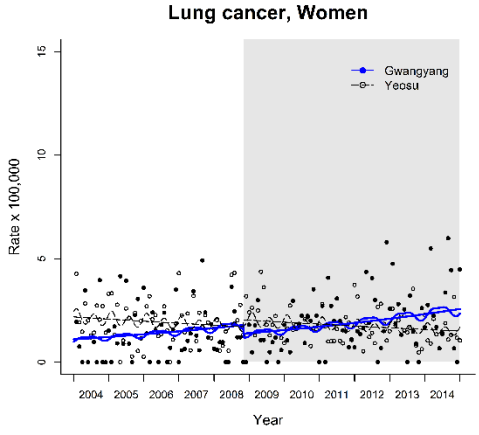

Irritant dermatitis, Women
Gwangyang
Yeosu
Rate x 100,000
Year

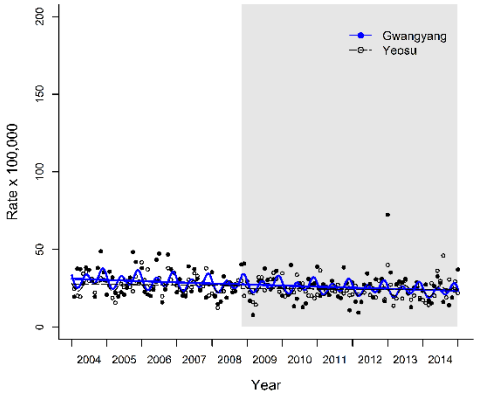

Other dermatitis, Women
Gwangyang
Yeosu
Rate x 100,000
0
100
200
300
400
500
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year


Unspecified dermatitis, Women
Gwangyang
Yeosu
Rate x 100,000
0
50
100
150
200
250
300
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year


Asthma, Women
Gwangyang
Yeosu
Rate x 100,000
0
200
400
600
800
1000
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year


Vasomotor and Allergic rhinitis, Women
Gwangyang
Yeosu
Rate x 100,000
0
500
1000
1500
2000
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year


Lung cancer, Women
Gwangyang
Yeosu
Rate x 100,000
0
5
10
15
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year


Humerus Fracture, Women
Gwangyang
Yeosu
Rate x 100,000
0
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2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year

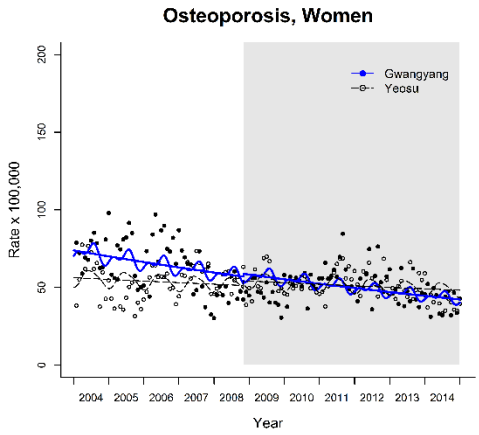


Figure 9. The association between the operation of the ferronickel factory (2008.11-) and the incidence of allergic and irritant disease in Gwangyang and Yeosu City women. Data points represent the monthly incidence rates of each disease in Gwangyang and the comparison city, Yeosu. Straight lines represent fitted estimates using a linear step change model, and the curved lines represent the seasonality adjusted model. The white and gray backgrounds represent the periods before (2004.01-2008.10) and after (2008.11-2014.12) the operation of the ferronickel factory.

Table 6. The association between the operation of the ferronickel factory (2008.11-) and the weighted incidence rate[a] of allergic and irritant disease in Gwangyang City.

Disease	Weighted monthly incidence rate[a] x 100,000		Relative risk (95% CI)
	Before (2004.01-2008.10)	After (2008.11-2014.12)	Step change
Men			
Pruritus	34.55	42.22	1.25 (0.92, 1.70)[b]
Acute bronchitis	1515.4	1739.39	1.03 (0.94, 1.12)[b]
Allergic contact dermatitis	503.79	525.29	0.98 (0.90, 1.06)[b]
Atopic dermatitis	234.3	243.83	1.17 (1.00, 1.36)[b]
Seborrheic dermatitis	79.15	77.32	1.07 (0.93, 1.22)[b]
Irritant contact dermatitis	69.69	71.33	1.09 (0.91, 1.31)[b]
Other dermatitis	119.34	133.25	0.97 (0.88, 1.08)[b]
Unspecified contact dermatitis	37.5	41.47	2.28 (1.37, 3.79)[b]
Asthma	323.72	378.88	1.13 (0.94, 1.35)[b]
Vasomotor and allergic rhinitis	617.34	673.45	1.27 (1.13, 1.43)[b]
Lung cancer	5.8	6.33	0.99 (0.64, 1.55)
Fracture of forearm	21.41	19.51	0.93 (0.77, 1.12)
Osteoporosis	4.62	2.34	0.92 (0.46, 1.81)

Women			
Pruritus	35.6	42.32	1.46 (1.14, 1.88)[b]
Acute bronchitis	1745.12	2033.84	0.95 (0.87, 1.04)[b]
Allergic contact dermatitis	574.37	587.63	0.97 (0.90, 1.03)
Atopic dermatitis	238.49	246.41	1.10 (0.95, 1.28)[b]
Seborrheic dermatitis	61.64	57.47	1.00 (0.85, 1.17)[b]
Irritant contact dermatitis	100.19	99.40	0.98 (0.85, 1.15)[b]
Other dermatitis	122.27	134.82	1.01 (0.89, 1.16)[b]
Unspecified contact dermatitis	52.34	60.32	2.47 (1.32, 4.63)[b]
Asthma	311.90	402.76	1.12 (0.93, 1.35)[b]
Vasomotor and allergic rhinitis	622.50	683.73	1.15 (1.04, 1.28)[b]
Lung cancer	4.37	6.09	0.64 (0.25, 1.62)
Fracture of forearm	26.95	26.66	1.08 (0.86, 1.36)
Osteoporosis	48.38	38.34	0.98 (0.81, 1.18)[b]

[a] Gwangyang City's incidence rate weighted by Yeosu City's incidence rate

[b] Breusch-Godfrey test revealed serial autocorrelation. Therfore, robust standard errors are used to calculate 95% confidence intervals

Table 7. Difference-in-difference (DID) analysis results which evaluated the association between operation of the ferronickel factory (2008.11-) and the incidence of allergic and irritant disease in Gwangyang and Yeosu City (Men).

Disease	Mean number of monthly incidence cases		Mean monthly incidence rate X 100,000		DID estimates
	Gwangyang	Yeosu	Gwangyang	Yeosu	Relative risk (95% CI)
Pruritus					
2004.11-2006.10	24.58	44.25	34	31.81	
2006.11-2008.10	27.96	54.88	36.04	35.75	0.94 (0.69-1.28)
2008.11-2010.10	32.63	70.71	51.25	45.91	1.04 (0.78-1.39)
2010.11-2012.10	45.58	64.79	76.56	43.73	1.64 (1.24-2.17)
2012.12-2014.10	41.92	71.58	66.3	50.37	1.23 (0.93-1.63)
Acute bronchitis					
2004.11-2006.10	541.58	1064.13	805.34	740.53	
2006.11-2008.10	404.83	834.54	588.4	593.89	0.91 (0.70-1.18)
2008.11-2010.10	382.71	678.96	582.33	519.56	1.03 (0.79-1.34)
2010.11-2012.10	371.75	597.88	582.97	490.04	1.09 (0.84-1.43)
2012.12-2014.10	352.29	495.92	522.21	428.95	1.12 (0.85-1.47)
Allergic contact dermatitis					
2004.11-2006.10	339.04	660.83	494.16	446.7	
2006.11-2008.10	306.33	503.92	430.59	360.55	1.08 (0.88-1.32)
2008.11-2010.10	281.54	456.88	401.86	343.66	1.06 (0.86-1.30)

2010.11-2012.10	284.38	435.46	401.96	331.8	1.10 (0.89-1.35)
2012.12-2014.10	245.21	386.13	351.25	298.95	1.06 (0.86-1.32)
Atopic dermatitis					
2004.11-2006.10	89.08	164.08	161.28	168.33	
2006.11-2008.10	77.29	127.29	143.49	134.99	1.11 (0.96-1.29)
2008.11-2010.10	71.67	107.96	142.29	125.22	1.19 (1.02-1.38)
2010.11-2012.10	64.88	91.71	127.68	118.83	1.12 (0.96-1.31)
2012.12-2014.10	52.63	83.29	101.53	112.05	0.95 (0.81-1.11)
Seborrheic dermatitis					
2004.11-2006.10	55.29	134.33	76.32	81.94	
2006.11-2008.10	56.75	153.79	73.72	99.13	0.80 (0.70-0.92)
2008.11-2010.10	57.5	144.21	75.54	92.75	0.87 (0.76-1.00)
2010.11-2012.10	62.71	148.08	80.2	97.74	0.88 (0.77-1.01)
2012.12-2014.10	60.42	137.46	78.49	92.79	0.91 (0.79-1.04)
Irritant contact dermatitis					
2004.11-2006.10	60.29	208.79	92.33	138.89	
2006.11-2008.10	59.21	219.92	85.67	151.72	0.85 (0.70-1.03)
2008.11-2010.10	49.5	163.08	76.9	121.56	0.95 (0.78-1.16)
2010.11-2012.10	58.13	165.33	90.53	131.4	1.04 (0.86-1.25)
2012.12-2014.10	57	163.88	87.79	132.05	1.00 (0.83-1.21)

Other dermatitis					
2004.11-2006.10	71.42	163.13	112.91	112.53	
2006.11-2008.10	88.08	167.21	137.04	118.96	1.15 (0.97-1.36)
2008.11-2010.10	80.33	164.75	134.44	120.3	1.11 (0.94-1.32)
2010.11-2012.10	95.38	171.79	167.51	131.24	1.27 (1.08-1.50)
2012.12-2014.10	104.04	187.96	184.53	154.67	1.19 (1.01-1.40)
Unspecified contact dermatitis					
2004.11-2006.10	36.54	68.46	51.38	45.86	
2006.11-2008.10	36.46	63.38	49.35	44.55	0.99 (0.71-1.38)
2008.11-2010.10	54.58	54.08	68.57	35.69	1.71 (1.23-2.40)
2010.11-2012.10	31.38	64	41.48	45.04	0.82 (0.58-1.16)
2012.12-2014.10	26.54	59.5	35.77	42.69	0.75 (0.53-1.06)
Asthma					
2004.11-2006.10	152.75	361.13	267.68	303.83	
2006.11-2008.10	95.38	346.96	157.19	279.92	0.64 (0.50-0.81)
2008.11-2010.10	111.83	297.21	196.53	263.04	0.85 (0.67-1.07)
2010.11-2012.10	105.83	224.08	181.84	226.8	0.91 (0.71-1.16)
2012.12-2014.10	100.63	170.63	175.16	186.2	1.07 (0.83-1.37)
Vasomotor and allergic rhinitis					
2004.11-2006.10	351.79	566.08	519.27	412.56	

2006.11-2008.10	321.63	614.29	479.53	458.61	0.83 (0.66-1.05)
2008.11-2010.10	340.63	544.13	539.96	420.55	1.02 (0.81-1.29)
2010.11-2012.10	313.58	408.33	494.84	349.37	1.13 (0.88-1.44)
2012.12-2014.10	273.42	392.13	437.82	356.71	0.98 (0.76-1.25)
Lung cancer					
2004.11-2006.10	4.25	10.54	6.84	6.21	
2006.11-2008.10	3.21	12.54	3.99	7.09	0.51 (0.36-0.73)
2008.11-2010.10	3.79	12	4.33	6.12	0.64 (0.45-0.92)
2010.11-2012.10	4.63	12	5.39	5.48	0.89 (0.63-1.26)
2012.12-2014.10	5.75	12.88	5.98	5.34	1.02 (0.72-1.44)
Fracture of forearm					
2004.11-2006.10	27.92	46.83	45.05	37.23	
2006.11-2008.10	27.96	45.25	43.05	36.6	0.97 (0.77-1.23)
2008.11-2010.10	25.17	41.04	35.95	33.73	0.88 (0.69-1.12)
2010.11-2012.10	25.21	37.42	36.98	31.17	0.98 (0.77-1.25)
2012.12-2014.10	21.88	38.75	32.89	32.88	0.83 (0.65-1.06)
Osteoporosis					
2004.11-2006.10	4.42	4.71	6.8	2.86	
2006.11-2008.10	8.75	12.25	11.03	6.93	0.67 (0.44-1.03)
2008.11-2010.10	10.04	17.33	12.2	8.63	0.60 (0.39-0.90)

2010.11-2012.10	11.71	20.54	13.56	9.16	0.62 (0.41-0.94)
2012.12-2014.10	8.17	18.75	8.2	7.47	0.46 (0.30-0.71)

Table 8. Difference-in-difference (DID) analysis results which evaluated the association between operation of the ferronickel factory (2008.11-) and the incidence of allergic and irritant disease in Gwangyang and Yeosu City (Women).

Disease	Mean number of monthly incidence cases		Mean monthly incidence rate X 100,000		DID estimates
	Gwangyang	Yeosu	Gwangyang	Yeosu	Relative risk (95% CI)
Pruritus					
2004.11-2006.10	21.21	43.83	29.57	29.13	
2006.11-2008.10	25.46	58.04	30.93	35.07	0.87 (0.63-1.20)
2008.11-2010.10	37.21	78.96	56.23	48.45	1.14 (0.85-1.53)
2010.11-2012.10	50.71	87.08	82.55	56.51	1.44 (1.09-1.91)
2012.12-2014.10	47.29	94.83	69.26	64.7	1.05 (0.80-1.40)
Acute bronchitis					
2004.11-2006.10	611.08	1173.54	942.98	831.96	
2006.11-2008.10	447.21	867.75	669.09	636.36	0.93 (0.72-1.19)
2008.11-2010.10	396.71	688.38	622.77	550.64	1.00 (0.77-1.29)
2010.11-2012.10	370.79	561.96	626.18	498.87	1.11 (0.85-1.44)
2012.12-2014.10	340.71	441.38	558.92	410.4	1.20 (0.91-1.58)
Allergic contact dermatitis					
2004.11-2006.10	397.83	813.88	597.18	546.56	
2006.11-2008.10	353.54	618.33	506.13	436.09	1.06 (0.88-1.29)
2008.11-2010.10	313.38	540.58	456.21	401.42	1.04 (0.86-1.27)

2010.11-2012.10	299.88	506.71	446.85	392.35	1.04 (0.86-1.27)
2012.12-2014.10	256.75	418.63	387.76	332.25	1.07 (0.87-1.31)
Atopic dermatitis					
2004.11-2006.10	95.13	174.13	179.34	185.99	
2006.11-2008.10	79.79	133.42	154.33	145.53	1.10 (0.98-1.24)
2008.11-2010.10	78.08	115.54	155.5	133.59	1.21 (1.07-1.36)
2010.11-2012.10	66.54	103.79	133.33	136.35	1.01 (0.90-1.15)
2012.12-2014.10	55.42	83.88	107.84	112.59	0.99 (0.87-1.13)
Seborrheic dermatitis					
2004.11-2006.10	46.42	106.88	66.84	71.93	
2006.11-2008.10	52.5	136.67	72.93	92.84	0.85 (0.74-0.97)
2008.11-2010.10	52.96	137.13	75.78	96.52	0.84 (0.74-0.97)
2010.11-2012.10	55.5	133.46	80.45	97.5	0.89 (0.77-1.02)
2012.12-2014.10	57.38	125.46	82.28	96.3	0.92 (0.80-1.05)
Irritant contact dermatitis					
2004.11-2006.10	87.96	246.46	135.84	161.24	
2006.11-2008.10	83.29	257.46	118.73	173.52	0.81 (0.67-0.98)
2008.11-2010.10	67.92	209.17	103.75	152.67	0.81 (0.67-0.98)
2010.11-2012.10	91.71	205.17	139.24	161.16	1.03 (0.85-1.23)
2012.12-2014.10	81.58	195	123.25	157.95	0.93 (0.77-1.12)

Other dermatitis					
2004.11-2006.10	75.92	171.5	121.13	121.84	
2006.11-2008.10	91.04	187.08	145.56	131.75	1.11 (0.90-1.37)
2008.11-2010.10	87.88	184.17	145.21	132.76	1.10 (0.89-1.35)
2010.11-2012.10	118.5	195.17	199.59	152.27	1.32 (1.08-1.61)
2012.12-2014.10	113.75	210.79	200.03	175.04	1.15 (0.95-1.40)
Unspecified contact dermatitis					
2004.11-2006.10	45.13	82.54	65.27	55.13	
2006.11-2008.10	45.29	82.67	59.06	56.28	0.89 (0.61-1.28)
2008.11-2010.10	70	72.71	86.06	47.25	1.54 (1.07-2.21)
2010.11-2012.10	43.46	96.38	55.61	63.67	0.74 (0.51-1.06)
2012.12-2014.10	40.63	84.33	52.73	60.59	0.74 (0.51-1.06)
Asthma					
2004.11-2006.10	175.54	436.33	296.42	346.42	
2006.11-2008.10	114.83	430.63	176.2	325.9	0.63 (0.49-0.82)
2008.11-2010.10	139.79	372.96	231.24	305.01	0.89 (0.69-1.13)
2010.11-2012.10	132.42	269.13	211.62	244.93	1.01 (0.78-1.31)
2012.12-2014.10	120.42	189.04	194.12	192.2	1.18 (0.90-1.55)
Vasomotor and allergic rhinitis					
2004.11-2006.10	404.71	686.92	621.01	502.58	

2006.11-2008.10	354.83	709.67	550.45	516.39	0.86 (0.68-1.10)
2008.11-2010.10	366.29	611.83	596.33	472.91	1.02 (0.80-1.30)
2010.11-2012.10	317.29	446.83	536.94	382.82	1.14 (0.88-1.46)
2012.12-2014.10	277	407.67	475.5	376.39	1.02 (0.79-1.32)
Lung cancer					
2004.11-2006.10	1.33	3.88	1.49	1.73	
2006.11-2008.10	1.54	4.96	1.43	2	0.83 (0.48-1.43)
2008.11-2010.10	1.63	5.08	1.38	1.99	0.80 (0.47-1.39)
2010.11-2012.10	1.88	4.88	1.85	1.73	1.23 (0.72-2.11)
2012.12-2014.10	3	4.75	2.51	1.6	1.81 (1.08-3.06)
Fracture of forearm					
2004.11-2006.10	19.42	45.29	30.3	28.08	
2006.11-2008.10	19.5	41.71	26.56	26.16	0.94 (0.74-1.19)
2008.11-2010.10	19.58	43.42	25.71	25.28	0.94 (0.74-1.19)
2010.11-2012.10	19.38	41.96	24.86	23.61	0.98 (0.77-1.24)
2012.12-2014.10	21.54	44.29	25.46	24.25	0.97 (0.77-1.23)
Osteoporosis					
2004.11-2006.10	61.25	108.88	73.49	48.45	
2006.11-2008.10	52.42	128.08	53.72	56.07	0.63 (0.54-0.73)
2008.11-2010.10	49.63	128	48.49	52.63	0.61 (0.52-0.71)

2010.11-2012.10	55.96	142.21	57.18	55.55	0.68 (0.59-0.79)
2012.12-2014.10	47.38	126.29	45.4	46.51	0.64 (0.55-0.75)

Table 9. The association between the operation of the ferronickel factory (2008.11-) and the incidence of allergic and irritant disease in Gwangyang City (by age group).

Disease	Mean number of monthly incidence cases		Mean monthly incidence rate[a] x 100,000		Relative risk (95% CI)
	Before (2004.01-2008.10)	After (2008.11-2014.12)	Before (2004.01-2008.10)	After (2008.11-2014.12)	Step change
Pruritus					
0 - 9	5.53	24.53	28.33	150.54	4.30 (2.66, 6.95)[b]
10 - 29	7.22	11.96	17.59	28.10	1.40 (1.09, 1.80)
30 - 59	25.76	31.14	41.00	43.84	1.01 (0.85, 1.20)[b]
60 -	11.83	16.68	68.14	82.65	0.97 (0.78, 1.21)
Acute Bronchitis					
0 - 9	245.91	198.82	1237.84	1214.91	1.19 (1.01, 1.41)[b]
10 - 29	243.26	150.34	597.66	350.61	1.04 (0.80, 1.36)[b]
30 - 59	431.88	322.00	689.83	455.54	0.84 (0.69, 1.03)[b]
60 -	107.91	67.28	645.67	333.67	0.90 (0.74, 1.10)[b]
Allergic dermatitis					
0 - 9	132.60	104.72	675.03	639.45	1.06 (0.96, 1.16)
10 - 29	172.10	134.59	420.38	314.84	1.04 (0.94, 1.16)
30 - 59	323.78	252.66	516.47	357.81	1.02 (0.93, 1.11)
60 -	91.52	61.95	541.43	308.37	1.02 (0.89, 1.16)[b]

Atopic dermatitis					
0 - 9	97.81	64.97	497.43	396.14	1.24 (1.12, 1.38)
10 - 29	39.74	26.93	97.31	63.01	0.99 (0.84, 1.15)[b]
30 - 59	33.03	28.49	52.68	40.36	1.06 (0.89, 1.27)[b]
60 -	7.45	8.28	43.52	41.01	1.18 (0.88, 1.56)
Seborrheic dermatitis					
0 - 9	9.41	11.54	48.92	70.43	1.43 (1.08, 1.88)[b]
10 - 29	30.00	38.01	73.00	89.37	0.94 (0.81, 1.09)
30 - 59	53.12	52.30	84.54	73.96	1.01 (0.91, 1.13)
60 -	12.86	13.20	76.66	65.72	1.09 (0.85, 1.39)[b]
Irritant contact dermatitis					
0 - 9	26.34	28.26	135.15	172.66	1.14 (0.94, 1.37)[b]
10 - 29	36.93	36.42	89.99	85.58	0.84 (0.70, 0.99)[b]
30 - 59	59.31	49.64	94.45	69.98	0.77 (0.66, 0.91)[b]
60 -	23.91	20.12	141.20	100.07	0.83 (0.66, 1.05)[b]
Other dermatitis					
0 - 9	48.50	70.38	250.64	430.41	0.98 (0.85, 1.12)[b]
10 - 29	35.14	41.82	85.25	98.10	1.03 (0.89, 1.19)
30 - 59	60.78	65.78	96.51	92.71	0.84 (0.75, 0.94)[b]
60 -	18.14	22.04	104.86	108.95	0.84 (0.71, 0.99)[b]

Unspecified contact dermatitis					
0 - 9	10.47	8.18	54.36	49.91	0.79 (0.60, 1.04)[b]
10 - 29	13.86	17.64	33.88	40.89	2.49 (1.24, 4.99)[b]
30 - 59	38.83	42.46	61.78	60.71	2.27 (1.29, 4.00)[b]
60 -	15.34	19.47	86.83	96.45	1.36 (1.03, 1.79)[b]
Asthma					
0 - 9	117.38	84.34	588.40	514.55	1.37 (1.10, 1.71)[b]
10 - 29	39.16	30.51	96.31	71.47	1.00 (0.75, 1.32)[b]
30 - 59	76.53	88.12	121.87	124.79	1.18 (0.95, 1.48)[b]
60 -	35.19	33.58	207.37	166.62	0.89 (0.73, 1.07)[b]
Vasomotor and allergic rhinitis					
0 - 9	169.07	185.84	864.30	1133.03	1.35 (1.17, 1.56)[b]
10 - 29	198.64	144.74	486.79	337.69	1.15 (0.98, 1.36)[b]
30 - 59	309.78	242.18	494.69	343.57	1.05 (0.90, 1.22)[b]
60 -	48.52	55.88	285.69	277.63	1.21 (1.01, 1.45)[b]
Lung cancer					
0 - 9	0.00	0.00	0.00	0.00	1.00 (0.50-2.01)
10 - 29	0.12	0.05	0.30	0.13	1.16 (0.07-19.28)
30 - 59	1.33	1.82	2.10	2.55	0.60 (0.36-1.02)
60 -	3.69	5.04	22.30	24.79	1.06 (0.73-1.55)

Fracture of forearm					
0 - 9	9.78	5.73	50.11	34.93	0.71 (0.54, 0.94)
10 - 29	18.78	16.43	45.72	38.40	1.06 (0.87, 1.28)
30 - 59	10.34	11.78	16.47	16.62	1.01 (0.79, 1.27)
60 -	8.76	10.38	51.81	51.36	1.03 (0.78, 1.37)
Osteoporosis					
0 - 9	0.02	0.00	0.09	0.00	-
10 - 29	0.48	0.22	1.21	0.51	1.98 (0.55-7.18)
30 - 59	24.14	19.76	38.75	27.88	1.24 (0.97-1.58)
60 -	37.72	40.66	218.96	202.52	0.98 (0.79-1.23)

[a]Monthly Incidence rate is calculated by dividing number of monthly incidence case with total number of annual population
[b]Breusch-Godfrey test revealed serial autocorrelation. Therfore, robust standard errors are used to calculate 95% confidence intervals

Table 10. The association between the operation of the ferronickel factory and the incidence of allergic and irritant disease in the sub-regions of Gwangyang. Jungma-dong and Geumho-dong are located within 10 km from the ferronickel factory and Gwangyang-eup is located over 15 km from the ferronickel factory.

Disease	Mean number of monthly incidence cases		Mean monthly incidence rate[a] x 100,000		Relative risk (95% CI)
	Before (2004.01-2008.10)	After (2008.11-2014.12)	Before (2004.01-2008.10)	After (2008.11-2014.12)	Step change
Pruritus					
Gwangyang-eup	11.55	19.69	25.96	41.28	1.51 (1.19, 1.92)[b]
Jungma-dong	14.26	38.72	36.62	89.62	1.93 (1.32, 2.83)[b]
Geumho-dong	5.14	5.91	26.11	59.68	1.81 (1.09, 3.01)[b]
Acute Bronchitis					
Gwangyang-eup	381.93	279.92	930.77	693.63	0.84 (0.71, 1.00)[b]
Jungma-dong	346.33	328.70	901.90	704.80	0.97 (0.82, 1.15)[b]
Geumho-dong	114.40	63.16	638.91	619.62	0.94 (0.69, 1.28)[b]
Allergic dermatitis					
Gwangyang-eup	201.33	189.62	468.06	435.75	0.99 (0.88, 1.12)[b]
Jungma-dong	228.09	219.89	582.99	455.16	1.02 (0.91, 1.16)[b]
Geumho-dong	85.29	59.07	468.38	432.62	1.10 (0.93, 1.30)[b]
Atopic dermatitis					
Gwangyang-eup	56.67	41.18	176.35	133.36	1.08 (0.94, 1.23)[b]

Jungma-dong	62.93	57.84	170.39	139.69	1.21 (1.07, 1.37)
Geumho-dong	22.02	10.11	155.60	108.82	0.89 (0.69, 1.14)
Seborrheic dermatitis					
Gwangyang-eup	37.41	38.05	83.06	84.86	0.88 (0.76, 1.03)[b]
Jungma-dong	28.81	41.08	70.49	82.01	1.11 (0.97, 1.27)
Geumho-dong	12.97	13.74	66.54	82.15	1.16 (0.90, 1.49)
Irritant contact dermatitis					
Gwangyang-eup	74.28	67.04	179.20	168.39	0.92 (0.80, 1.05)
Jungma-dong	23.62	30.68	61.39	66.83	1.00 (0.84, 1.19)
Geumho-dong	9.05	8.09	53.91	63.18	0.80 (0.58, 1.12)[b]
Other dermatitis					
Gwangyang-eup	41.83	65.28	101.53	176.48	1.09 (0.96, 1.24)
Jungma-dong	57.40	75.66	147.31	174.81	0.85 (0.75, 0.97)
Geumho-dong	18.43	19.65	113.66	185.99	0.94 (0.74, 1.19)
Unspecified contact dermatitis					
Gwangyang-eup	38.47	26.16	82.40	54.23	0.65 (0.52, 0.81)[b]
Jungma-dong	10.57	24.76	28.79	47.87	5.58 (2.37, 13.13)[b]
Geumho-dong	3.55	7.39	22.07	43.89	4.90 (2.39, 10.03)[b]
Asthma					
Gwangyang-eup	79.09	69.01	214.72	175.80	0.89 (0.71, 1.10)[b]

Jungma-dong	88.50	104.65	242.65	241.63	1.48 (1.15, 1.90)[b]
Geumho-dong	31.09	17.22	207.85	171.90	1.15 (0.76, 1.75)[b]
Vasomotor and allergic rhinitis					
Gwangyang-eup	181.19	208.76	438.53	535.50	0.99 (0.84, 1.17)[b]
Jungma-dong	293.95	286.18	736.62	624.45	1.23 (1.08, 1.41)[b]
Geumho-dong	98.72	65.93	549.62	575.25	0.99 (0.84, 1.18)[b]
Fracture of forearm					
Gwangyang-eup	12.34	12.85	30.93	28.66	0.99 (0.79, 1.26)
Jungma-dong	13.41	14.20	38.15	30.84	0.87 (0.72, 1.06)
Geumho-dong	6.90	5.51	41.31	34.33	0.79 (0.55, 1.13)

[a] Age standardised according to WHO standard population
[b] Breusch-Godfrey test revealed serial autocorrelation. Therfore, robust standard errors are used to calculate 95% confidence intervals

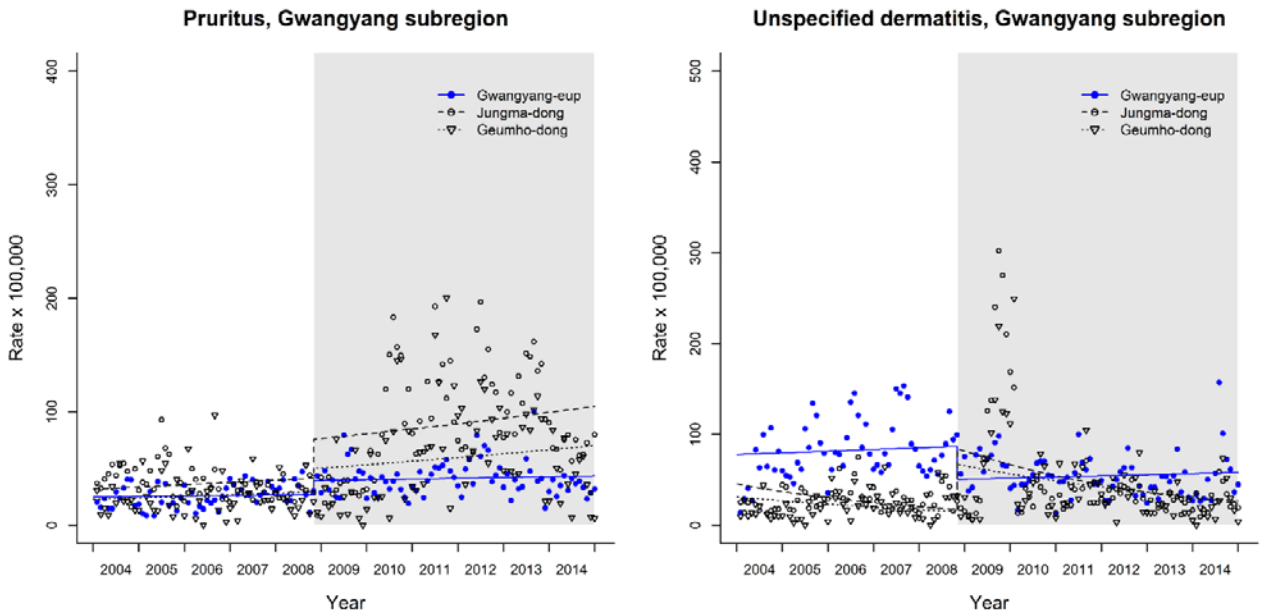


Figure 10. The association between the operation of the ferronickel factory (2008.11-) and the monthly incidence of pruritus and unspecified contact dermatitis in the sub-regions of Gwangyang City. Data points represent the monthly incidence rates of each disease in the sub-regions of Gwangyang. Jungma-dong and Geumho-dong are located within 10 km from the ferronickel factory and Gwangyang-eup is located over 15 km from the ferronickel factory. Straight lines represent fitted estimates using a linear step change model. White and gray backgrounds represent periods before (2004.01-2008.10) and after (2008.11-2014.12) the operation of the ferronickel factory.

Discussion

Summary of the study findings

Public concern regarding the adverse health effects of the ferronickel manufacturing factory on residents has been raised since the factory started its operation. Our study results showed abrupt increases in the monthly incidence of pruritus, atopic dermatitis, asthma, and vasomotor and allergic rhinitis among Gwangyang City residents after the opening of the factory. These findings were shown in both men and women, and the magnitude of the increase was greater in children (aged 0-9). In addition, an abrupt short-term increase in the monthly incidence of unspecified contact dermatitis was observed among Gwangyang City residents in the summer of 2009, several months after the factory opening.

By comparing the disease incidence patterns of Gwangyang City with the comparison city, Yeosu, we found a significant difference in the effects of ferronickel factory operation on unspecified contact dermatitis and vasomotor and allergic rhinitis in men, and pruritus, unspecified contact dermatitis, and vasomotor and allergic rhinitis in women. Yeosu City residents showed a null association between the operation of the ferronickel factory and changes in irritant or allergic disease incidence patterns except for pruritus. These findings support the consistency and specificity of the association between the ferronickel factory operation and the increase in irritant or allergic disease incidence among Gwangyang City residents.

In the stratified analysis of the sub-regions of Gwangyang City, the increase of irritant

or allergic disease incidence was greater among residents living near the ferronickel factory compared to those living far from the factory. The abrupt short-term increase in the incidence of unspecified contact dermatitis in the summer of 2009 was observed among Gwangyang City residents living near the ferronickel factory, but not among Yeosu City residents or Gwangyang City residents living far from the factory. These findings suggest a biological gradient for the association between the changes in the disease incidence patterns and the distance from the ferronickel factory.

Plausible biological mechanisms

Nickel, cobalt, and chromium were detected from the air, soil, and water sediments near ferronickel manufacturing factories and ferronickel mines in previous studies (Bačeva et al. 2012; Boev et al. 2013; Marrugo-Negrete et al. 2017; Marrugo-Negrete et al. 2014). By analyzing attic dust samples collected from houses located near a ferronickel smelter plant, over 90% of the mineral constituents present in the ferronickel ore (serpentine and amphibole group of minerals), which are uncommon constituents of urban dust, were present in the attic dust samples (Boev et al. 2013). In addition, higher contents of nickel, cobalt, and chromium were detected in the attic dust sample when compared to the natural contents of soil and rocks from the surrounding region (Bačeva et al. 2011; Boev et al. 2013). By using a moss biomonitoring method, moss samples near the ferronickel smelter plant were found to have a higher content of nickel, cobalt, and chromium (Bačeva et al. 2012).

Particularly, the content of nickel was 31 times higher in the moss samples collected from the vicinity of the ferronickel plants compared to the moss samples collected from the entire territory of the Republic of Macedonia.

These previous studies suggest the ferronickel manufacturing factory as an important source of airborne heavy metal particles near the ferronickel factory. According to the Pollutant Release and Transfer Registry, there were abrupt increases in the amount of nickel waste transfer and air emissions of nickel, chromium, and their compounds in Gwangyang City after the ferronickel factory operation (Ministry of Environment 2018). In a report from the National Institute of Environmental Research, the Republic of Korea, the levels of nickel and chromium were higher in the atmosphere of Gwangyang's sub-regions near the ferronickel factory compared to sub-regions of Yeosu (Table 2). Therefore, it is reasonable to speculate that the nickel and other heavy metal contents of Gwangyang City's airborne particles are affected by the ferronickel manufacturing factory.

Nickel, cobalt, and chromium are heavy metals which are causal agents for airborne contact dermatitis (Huygens and Goossens 2001). Lime (CaO) and magnesia (MgO) in ferronickel slag may increase the pH when ferronickel slag is dissolved in water (Demotica et al. 2012). In addition, crystalline, glassy, and rough regions are observed in the microstructure of ferronickel slag (Demotica et al. 2012). Probably, the alkalinity and abrasive surface of ferronickel slag may have contributed to the skin irritation after exposure to ferronickel slag dust.

Several occupational studies have reported a possible association between heavy metal dust exposure and allergic skin symptoms and asthma. Nickel contact dermatitis is a common disease among industrial workers who handle raw nickel materials (Blanco-Dalmau et al. 1984; Lidén 1994). A worker from a metallurgical laboratory suffered highly pruritic rosacea-like symptoms after the airborne nickel exposure (Kanerva et al. 1999) and cement dust containing chromate caused allergic skin symptoms (Sayed and Bazex 1994). Nickel sulfate and chromium in workplace dust are common sensitizing agents, which might induce asthma by inhalation (Block and Yeung 1982). In addition, serum immunoglobulins were elevated in workers occupationally exposed to nickel and cobalt when compared to age-matched control groups (Bencko et al. 1982). Therefore, occupational exposure to heavy metals and occurrence of the allergic and irritant symptoms are anticipated for field workers of the ferronickel factory. In addition, an abrupt increase in unspecified contact dermatitis just after the ferronickel factory operation was not shown among 0-9-year-old children group, who are less likely to be occupationally exposed to the heavy metals. Because field worker tends to reside near the factory, greater increase of allergic or irritant disease among residents living near the ferronickel factory also supports the hypothesis that occupational exposure is one of the explanations for our study findings.

On the other hand, the entire city residents can be exposed to relatively low levels of heavy metal dust after the operation of the ferronickel factory. In this case, our situation might be more similar to meteorological events, such as an Asian dust,

which affect large numbers of the population with low levels of airborne heavy metals. Asian dust usually occurs during the spring or fall in the East Asian region. The dust which originates from the Chinese and Mongolian deserts adsorbs diverse anthropogenic materials such as environmental pollutants, microbiological materials, and heavy metals during their transportation (Onishi et al. 2012).

Asian dust exposure is associated with diverse forms of acute allergy-related conditions such as skin symptoms, allergic rhinitis, asthma, and conjunctivitis (Otani et al. 2012). Allergic reactions after Asian dust exposure are believed to be derived from the heavy metal particles bound to the dust (Otani et al. 2012). Particularly, nickel contents are highly associated with skin symptoms and subjects with skin symptoms after Asian dust exposure showed the tendency for nickel allergies (Onishi et al. 2012; Onishi et al. 2015; Otani et al. 2012). In addition, exposure to Asian dust particles was associated with increased respiratory inflammation in rats (Lei et al. 2004). In in vitro studies, metallic components of Asian dust were associated with respiratory inflammation, and particularly, nickel showed a high affinity for the horny layer and inner root sheath of hairs of normal skin (Shin et al. 2013; Wells 1956). 5% nickel sulfate and 1% cobalt chloride caused irritation in individuals under the occlusion patch tests (Kalimo and Lammintausta 1984), and 0.1% nickel sulfate solution caused irritation on scarified skin after exposure once daily for 3 days (Frosch and Kligman 1976).

Therefore, it is biologically plausible to explain that exposure to the heavy metal-containing dust originating from the ferronickel factory and ferronickel slag disposal site may have increased the incidence of irritant or allergic disease among residents. However, there are several findings which need additional explanation. First, the monthly incidence of pruritus showed a marked increase since early 2010, thereby showing about 1-year time lag after the operation of the ferronickel factory. Although nickel-induced contact dermatitis needs sensitization before the occurrence of skin symptoms and exposure to nickel in ambient air has been associated with nickel sensitization among children (Mann et al. 2010), we were unable to find similar study which explains a possible association between heavy metal dust exposure and pruritic skin symptoms with such a time lag. In addition, overall patterns of monthly incidence of allergic dermatitis (ICD-code: L23.X) which contains allergic contact dermatitis due to metals (L23.0) did not show any marked change after the factory operation, which suggests that pruritic skin symptoms of Gwangyang City residents may not have appeared as typical nickel or chromium related allergic contact dermatitis (Figure 8 and Figure 9).

Second, statistically significant increase in pruritus incidence after the ferronickel factory operation in Yeosu City residents are unexpected results. Although we selected nearest industrial City, Yeosu to increase overall comparability, Yeosu City residents may not serve as an absolute counterfactual scenario of Gwangyang City residents (what if the disease incidence rate changed in Gwanyang City residents if there was no ferronickel factory opening in Gwangyang City) due to the spillover

effects of ferronickel factory and comparability issues.

Two to three sub-regions of Yeosu City are geographically close to Gwangyang City and can be affected by the ferronickel factory (Figure 4). Although the additional sub-regional level analysis in Yeosu City are needed to verify this hypothesis, we may get some clues from the seasonal analysis. In Gwangyang City, southern and northwestern winds are dominated during the summer and winter, respectively (National Institute of Environmental Research (NIER) 2012) (Figure 11). Because the ferronickel factory is located at Geumho-dong, at the southeastern part of Gwangyang City, Gwangyang City residents may be exposed more frequently to the airborne heavy metal dust originating from the factory and slag disposal site in summer compared to winter. In contrast, because Yeosu City is located on the southern side of Gwangyang City, Yeosu City residents may be exposed more frequently to the airborne heavy metal dust in winter compared to summer due to the dominated wind flow from the north in winter.

In a sensitivity analysis by season (summer: June to August; winter: December to February), the effect size of relative risk estimates for an abrupt increase of monthly pruritus, atopic dermatitis, unspecified contact dermatitis, and vasomotor and allergic rhinitis incidence rates of Gwangyang City after the factory operation were higher in summer compared to winter (Figure 12). In addition, we observed increased relative risk estimate for an abrupt increase of monthly pruritus incidence rate of Yeosu City in winter compared to summer. However, follow up studies with sub-regions of Yeosu City and epidemiological surveys for Gwangyang and Yeosu City residents are

needed to verify the causal association between ferronickel factory operation and increase of allergic and irritant disease of local residents.

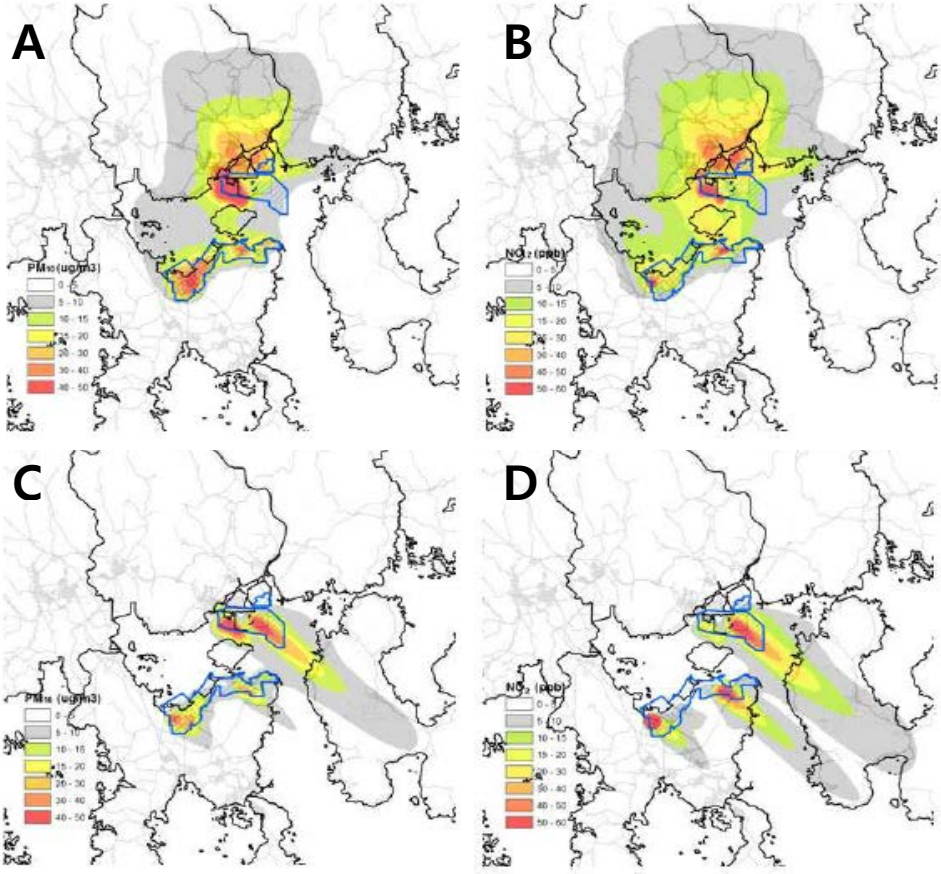
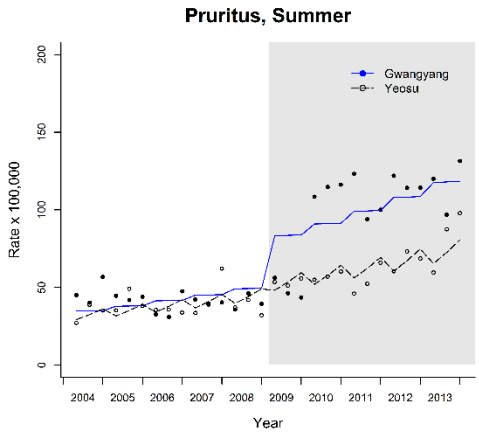
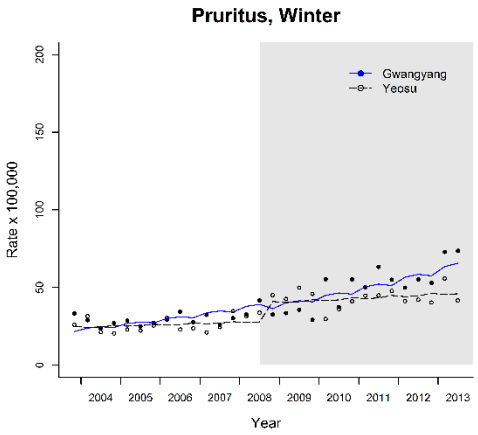
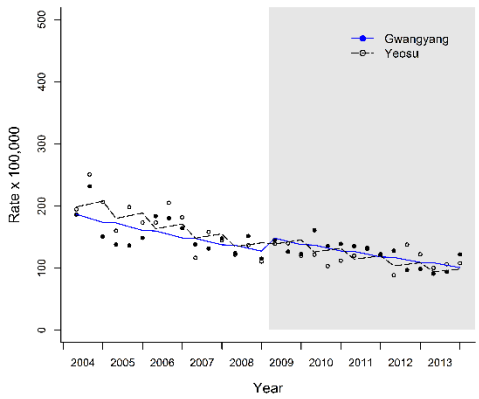
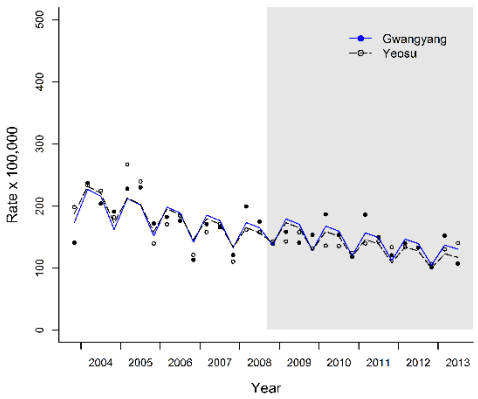


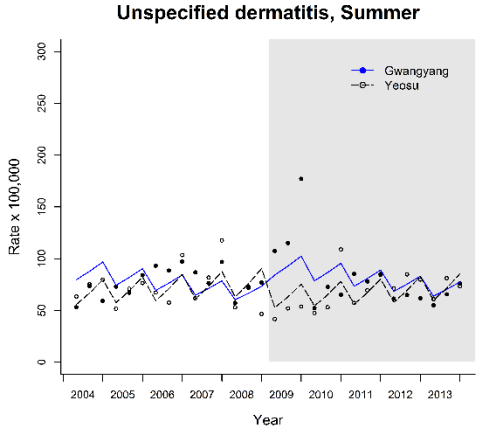
Figure 11. Monthly average air pollution concentration modelling results of Gwangyang Bay region for year 2012 (A: July, PM_{10}; B: July, NO_2; C: January, PM_{10}; D: January, NO_2). The figures are from the report titled "Monitoring of Exposure of Environmental Pollutants and Health Effects of Inhabitants in Industrial Complexes, Gwangyang Bay, 2nd stage, first year" (National Institute of Environmental Research (NIER) 2012).

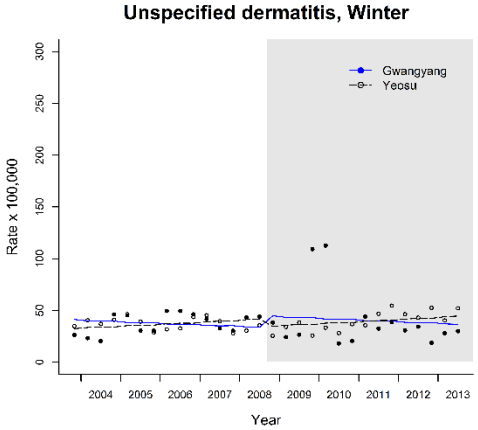

Pruritus, Summer
Gwangyang
Yeosu
Rate x 100,000
Year


Pruritus, Winter
Gwangyang
Yeosu
Rate x 100,000
Year


Atopic dermatitis, Summer
Gwangyang
Yeosu
Rate x 100,000
Year


Atopic dermatitis, Winter
Gwangyang
Yeosu
Rate x 100,000
Year


Unspecified dermatitis, Summer
Gwangyang
Yeosu
Rate x 100,000
Year


Unspecified dermatitis, Winter
Gwangyang
Yeosu
Rate x 100,000
Year

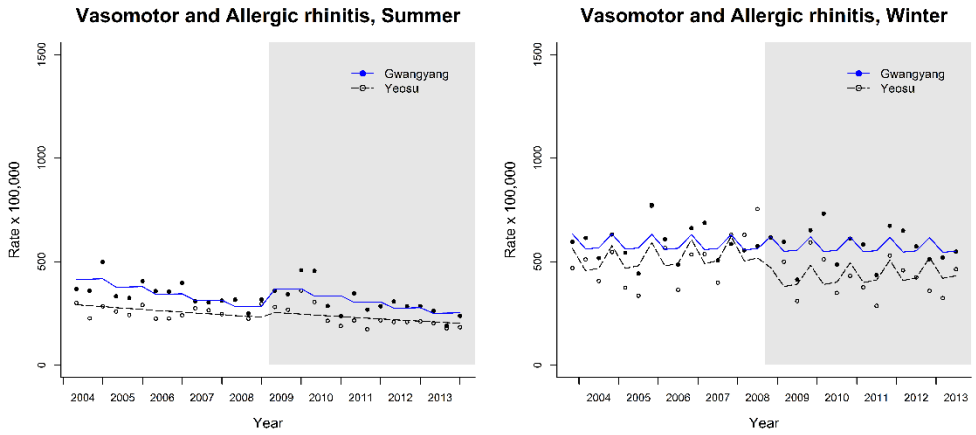


Figure 12. The association between the operation of the ferronickel factory (2008.11-) and the monthly incidence of pruritus, atopic dermatitis, unspecified contact dermatitis, and vasomotor and allergic rhinitis in Gwangyang and Yeosu City. Analyses were conducted separately by season (summer: June to August; winter: December to February). To match same number of time-series before and after the ferronickel manufacturing factory operation, we adjusted the study period from December 2003 to November 2013. Data points represent the monthly incidence rates of each disease in Gwangyang and Yeosu City. Curved line represent the seasonality adjusted model. The white and gray backgrounds represent the periods before (2003.12-2008.10) and after (2008.11-2013.11) the operation of the ferronickel factory.

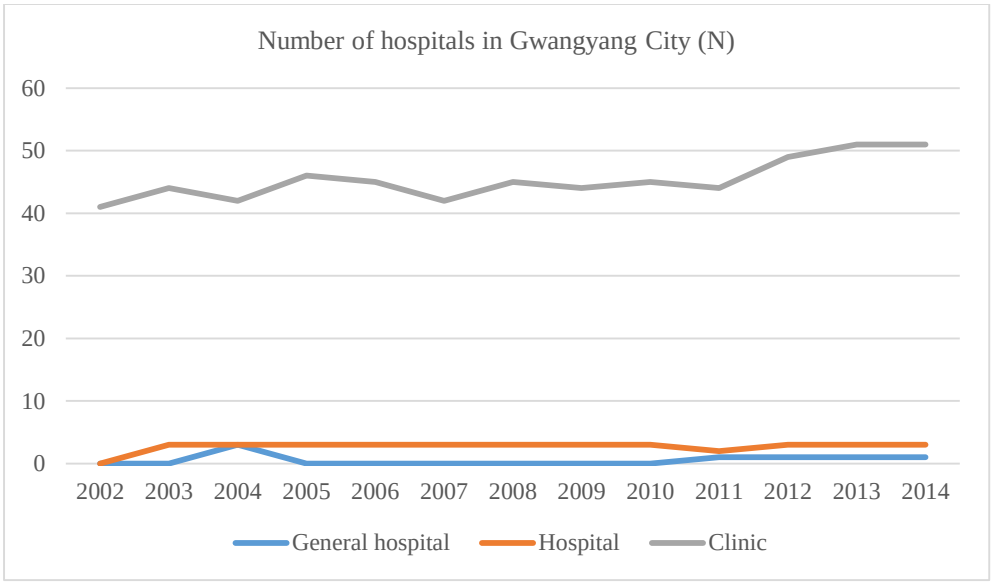
Strengths and limitations

There are several limitations in our study. First, there could be changes in other unknown time-varying confounders which occurred during the opening of the ferronickel factory (Bernal et al. 2016). For example, air pollution other than particulate matter or other socioeconomic variables of Gwangyang City residents could have changed around the opening of the factory. Because the Gwangyang City industrial complex is composed of series of steel mill and other related industries, changes in production amounts, changes in manufacturing processes, or opening of new industries which may coincide with the operation of the ferronickel factory can affect our study results. In addition, accessibility to the hospital may be increased if the number of hospitals and doctors were simultaneously increased with the operation of the factory. However, to minimize the effects of other unknown time-varying confounders, we added a control region and control outcomes in our interrupted time-series design (Lopez Bernal et al. 2018). Furthermore, the number of doctors and hospitals did not change with the operation of the ferronickel factory in the Gwangyang City (Figure 13) and additional adjustment for yearly numbers did not change our study results. However, even with our study design, there is the possibility that circumstances unique to Gwangyang City may have affected our study findings. For example, we do not have detailed daily heavy metal content information of particulate matter or meteorological data (wind speed, direction, temperature, and humidity) in the sub-regions of Gwangyang City during our study period which might have affected the results of the sub-regional level analysis.

Second, in our subgroup analysis, several subgroups comprised of relatively small populations may produce unstable incidence rates. This could lead to a reduction in the statistical precision of our estimates in the subgroup analysis. Third, although we used ICD-10 codes to determine the incident cases of asthma, allergic rhinitis, and dermatitis, the diagnostic accuracy of each disease had not been confirmed in the health insurance claim data. However, these potential non-differential misclassifications may not have affected our study conclusion seriously, since such misclassifications are more likely to pull the results toward the null. Fourth, because we used health insurance claim data for over 10 years of the study period, changes in administrative procedure may have affected the registered data. However, we found relatively stable incidence patterns in several allergic diseases such as allergic dermatitis and the control outcomes, fracture of the forearm and osteoporosis, which suggests minimal effects of instrumentation in our study.

Even if the validity of our study is threatened by the above limitations, there are two important findings which suggests the possible association between the ferronickel factory operation and the changes in the disease incidence patterns among Gwangyang City residents. First, the monthly incidence of pruritus and vasomotor and allergic rhinitis had increased in Gwangyang City after the opening of the ferronickel factory, and these increases were significant even after accounting for the changes of the corresponding disease incidence of the comparison city, Yeosu. Second, there was an unusual short-term increase in unspecified contact dermatitis in the summer of 2009 in Gwnagyang City, and this increase was seen among residents

from Gwangyang City's sub-regions near the factory site but not in the sub-regions far from the factory or in the comparison city, Yeosu.



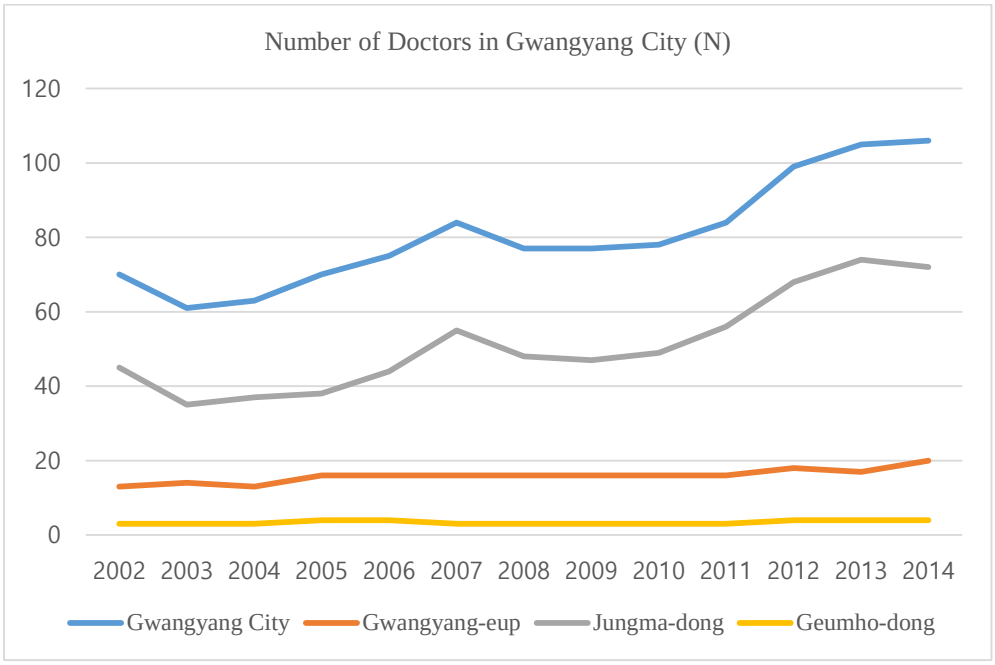


Figure 13. Temporal trends in yearly number of doctors and hospitals in Gwangyang City from 2002 to 2014

Future study using the National Health Insurance data

Exposure to the pollutants originating from the industrial complex may affect the health status of the local residents. In addition, specific events such as opening of the factories or the accidents occurred in the industrial complex may lead to specific disease development. Therefore, health and exposure status of the local residents residing near the national industrial complexes should be routinely monitored (Bae et al. 2018).

Fortunately, Korea is maintaining a unique health insurance system which archives all the hospital use data of almost entire population. By carefully analyzing the hospital use patterns of the local residents, we may able to get clues regarding the health effects of the industrial complexes. By using the study design and statistical approach used in our study, we may also able to assess adverse health effects of specific event or accidents occurred in the industrial complexes. In addition, our methods can be used to evaluate the potential health effects of governmental policy (e.g. four-river refurbishment project) or natural disasters (e.g. an earthquake in Pohang City in year 2017 or a forest fire in Goseong county in year 2019) occurred in Korea. Selecting an appropriate control region and control outcome may increase the validity of the study findings.

Conclusion

Our study suggests possible association between the operation of the ferronickel factory and an abrupt increase of pruritus, unspecific contact dermatitis, and vasomotor and allergic rhinitis in Gwangyang City residents. We used interrupted time-series analysis, one of the quasi-experimental analysis methods, to evaluate possible association between ferronickel factory and its adverse health effects. Our study finding may serve as evidences for the future community-based epidemiological survey in Gwangyang City.

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초록

시계열분석을 활용한 페로니켈공장의 지역사회 건강영향 평가

한창우

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배경: 2008년 10월 전라남도 광양시에 개소한 페로니켈공장은 스테인리스강 제품의 원료로 사용되는 페로니켈을 연간 30,000 톤씩 생산하고 있음. 지역주민들은 페로니켈 생성과정 및 슬래그 야적장에서 비산하는 먼지의 건강 영향에 대한 우려를 나타냄. 이에 본 연구에서는 절단적시계열 분석방법을 사용하여, 페로니켈공장 개소 후 광양시 천식, 알레르기 비염, 피부염의 발생이 그 전과 비교하여 유의미하게 증가하였는지 평가하고자 함.

방법: 본 연구를 위해 광양시 주민들의 2002-2014년도 천식, 알레르기 비염, 피부염 관련 의료이용 정보를 국민건강보험 데이터베이스에서

추출함. 계절성을 보정한 분절성 포아송 회귀 분석을 활용하여 페로니켈공장의 가동이 광양시 주민들의 질병 발생에 영향을 주었는지 평가함. 천식, 알레르기 비염, 피부염 관련 의료이용의 증가가 페로니켈공장이 위치한 광양시에서만 나타남을 증명하기 위해, 광양시 인근 여수시를 대조지역으로 선정하여 동일한 분석을 수행함. 또한 광양시 세부 지역별 분석을 통해, 공장과의 거리가 질병 발생에 영향을 주는지 평가함.

결과: 분석 결과 광양시 거주 남성의 경우, 페로니켈공장 개소 전과 비교하여, 개소 후 상세 불명의 접촉피부염 [상대위험도 (RR) (95%CI): 1.75 (1.17-2.60)]과 혈관운동성 및 알레르기성 비염 [RR (95%CI): 1.23 (1.08-1.39)]의 발생이, 여성의 경우 가려움 [RR (95%CI): 1.95 (1.51-2.52)], 상세 불명의 접촉피부염 [RR (95%CI): 1.65 (1.04-1.31)], 혈관운동성 및 알레르기성 비염 [RR (95%CI): 1.17 (1.04-1.31)]의 발생이 통계적으로 유의하게 증가한 것으로 나타남. 이러한 증가는 대조지역인 여수시의 질병 발생 변화를 보정한 이후에도 동일하게 나타남. 연령별 층화분석 결과 질병발생 증가는 0-9 세 어린이들에서 크게 나타났으며, 광양시 세부지역별 분석에서는 페로니켈 공장에서 가까운 곳에 거주하는 주민들이 먼 곳에 거주하는 주민들에 비해 공장 개소 이후 질병 발생의

증가 정도가 더 큰 것으로 나타남.

결론: 과거 해당 지역에서 수행된 산업단지 건강영향 조사는 단면적인 설문조사에 국한되어 옴. 본 연구는 절단적시계열 분석이라는 준실험적 연구방법론을 사용하여, 페로니켈 공장의 지역주민에 대한 건강영향을 인과적으로 추정하고자 하였음. 본 연구 결과를 바탕으로 향후 광양시에서 수행 가능한 지역사회 역학 조사를 설계할 수 있을 것으로 사료됨. 특히 알레르기 및 피부 자극 질환, 어린이 질환에 집중하여 조사를 수행한다면 공장의 지역사회 주민 건강 영향에 관한 유의미한 결과를 도출할 수 있을 것으로 사료됨.

주요어: 페로니켈공장; 니켈; 절단적시계열분석; 가려움증; 피부염; 비염

학 번: 2016-35108

Conflict of Interest

The authors declare no conflict of interest. Authors did not have any contact with local residents, private organizations, or the ferronickel manufacturing company during any parts of this study.

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